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Review

Super-enhancers: A new frontier for glioma treatment

Meng Cheng[a,b,1], Zheng Wei Zhang[a,b,1], Xing Hu Ji[a,b,1], Yadi Xu[a,b], Erbao Bian[a,b,*], Bing Zhao[a,b,*]

[a] Department of Neurosurgery, The Second Affiliated Hospital of Anhui Medical University, Hefei 230601, China
[b] Cerebral Vascular Disease Research Center, Anhui Medical University, Hefei 230601, China

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ABSTRACT

Glioma is the most common primary malignant tumor in the human brain. Although there are a variety of treatments, such as surgery, radiation and chemotherapy, glioma is still an incurable disease. Super-enhancers (SEs) are implicated in the control of tumor cell identity, and they promote oncogenic transcription, which supports tumor cells. Inhibition of the SE complex, which is required for the assembly and maintenance of SEs, may repress oncogenic transcription and impede tumor growth. In this review, we discuss the unique characteristics of SEs compared to typical enhancers, and we summarize the recent advances in the understanding of their properties and biological role in gene regulation. Additionally, we highlight that SE-driven lncRNAs, miRNAs and genes are involved in the malignant phenotype of glioma. Most importantly, the application of SE inhibitors in different cancer subtypes has introduced new directions in glioma treatment.

1. Introduction

Glioma is one of the most common types of primary malignant tumors and accounts for more than 30% of all primary brain tumors [1]. Over the past several decades, glioma has been characterized by necrosis, aggressive growth, and angiogenesis [2]. The World Health Organization (WHO) has divided glioma into four types based on morphological characteristics and prognosis [3]. Low-grade gliomas (Grades I and II) mainly contain astrocytomas, oligodendrogliomas, pleomorphic xanthoastrocytomas, and certain ependymomas that are well-differentiated and have low malignancy [4]. High-grade gliomas (Grades III and IV) include anaplastic astrocytomas, anaplastic oligodendrogliomas, glioblastoma multiforme, and anaplastic oligodendrogliomas that are poorly differentiated and highly malignant [5]. High-grade gliomas account for the majority of all gliomas, and they are heterogeneous and consist of tumor cells, glioma-like stem cells, a wide range of blood vessels and immune cells [6–8]. Currently, the main therapies for glioma include surgical resection, oral alkylating agents and radiation [9]. Despite great advances in therapeutic interventions against glioma, the prognosis of patients with glioma remains poor [10]. Therefore, there is an urgent need to identify the underlying molecular mechanisms of glioma development.

Super-enhancers (SEs) are ultra-long cis-acting elements with enhanced transcriptional activity [11]. SEs are a type of hyperactive regulatory domain that comprises many complex regulatory elements [12]. These regulatory elements work together to regulate key gene networks involved in cellular identity [13]. Recently, SEs have been found to play a central role in gene transcription activation in different types of cells and to be involved in the pathological processes of numerous tumors including glioma [14,15]. Although the effect of SEs has been verified in many tumor cells, their specific regulatory mechanisms have not been thoroughly studied. Increasing evidence has suggested that transcriptional dysregulation caused by SEs has potential effects on the biological function of glioma [16–18]. Previous studies have shown that abnormal transcription of protein-encoded genes, including the inactivation of tumor suppressor genes and the activation of proto-oncogenes, plays a necessary role in the development of glioma [19,20]. Interestingly, an increasing number of studies has focused on the transcriptional dysregulation of non-coding RNA (lncRNA and miRNA) in the pathology of glioma [21–23]. In this review, we will explore the structure and function of SEs, and we illustrate their relationship with protein-coding genes and non-coding genes (lncRNA and miRNA) in glioma.

* Corresponding authors at: Department of Neurosurgery, the Second Affiliated Hospital of Anhui Medical University, Cerebral Vascular Disease Research Center , Anhui Medical University, 678 Fu Rong Road, Hefei, Anhui Province 230601, China.
E-mail addresses: aydbeb@126.com (E. Bian), aydzhb@126.com (B. Zhao).
[1] This author contributes equally to the first author.

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2. Overview of super enhancers

2.1. What are SEs?

Enhancers are a class of cis-acting DNA elements that typically form long chromatin rings with target genes [24]. Enhancers can precisely regulate the expression of target genes even when they are far away from target genes, and enhancers play a regulatory role in cell differentiation and development [25]. There are several transcription factor (TF)-binding sites on enhancers, which are implicated in regulating the activity of enhancers [26]. The regulatory mechanism of enhancers has been well studied in many tumors, including glioma [25,27,28]. In 2013, Whyte et al. proposed the concept of SEs for the first time based on the study of enhancers [29]. Despite the widespread belief that SEs are unique and regulate the expression of key identity genes in cells, there is an alternative view held by some researchers that SEs are just clusters of enhancers [30,31]. These kinds of enhancers cluster together and work similarly to typical enhancers, contributing an additive effect on their target genes. Given this controversy, it is necessary to explore the structural composition of SEs and their functional patterns. In certain regions of SEs, there are hotspots occupied by multiple genealogy-specific TFs, which generally span tens of bases of extended histone modification markers covered with active enhancers [32]. In addition, SEs are heavily loaded with chromatin remodelers, transcription co-activators, and Pol II holoenzyme by at least one order of magnitude greater than typical enhancers [29], which creates super strong transcriptional activity and specific biochemical characteristics (Fig. 1). SEs were first identified in mouse embryonic stem cells (ESCs) and defined the identity of ESCs by strongly enriching ESC-specific TFs, such as OCT4, NANOG and SOX2 [29]. Subsequently, based on the enrichment of master TFs in cell type-specific genes that determine the biological function of cells, more SEs have been identified in different cell types [13]. However, the current definition and understanding of SEs in cells are not clear.

2.2. Characteristics of SEs

Increasing evidence shows that SEs are occupied by components, including TFs, chromatin regulators, coactivators, and RNA polymerase II complex, which are associated with enhancer activity [11]. In addition, SEs are unique in that the average density of these components at the SE locus is 10 times that of typical enhancers [33]. As important cis-acting regulatory elements in the cellular identity and development of multicellular organisms, enhancers regulate gene expression by acting on nearby promoters [34]. For example, the enhancers that encode upstream of the β-globulin gene in HeLa cells increase the expression of the β-globulin gene by 200-fold [35]. In the model defined by Whyte et al., SEs are an ultralong cis-acting element 8-20 kb in length with transcription-enhancing activity that gathers key TFs and their cofactors in high density. Compared to typical enhancers, SEs have stronger transcriptional activation ability, and their associated genes show higher expression levels [15,36]. As a result, we suggest that SEs may strongly promote the transcription of their target genes. In addition, SEs not only affect gene expression with their component enhancers but also have an effect on the functional levels within the constitutive enhancers [31,37]. The further distinction between SEs and typical enhancers highlights the interaction of their components and their ability to function as a unit. Increasing evidence suggests that SEs have some unique characteristics compared with typical enhancers [15,38]. The following aspects are the unique characteristics of SEs that distinguish them from typical enhancers: (i) SEs enrich a large number of TFs, cofactors and histone markers (H3K27ac and H3K4me1) associated with transcription activity [39,40]; (ii) SEs span a larger genomic region with the median size of SEs ranging from 10 kb to over 60 kb [15,29]; (iii) SEs can define a cell identity and drive the expression of oncogenes [36,41,42]; (iv) SE-driven genes have high abundance and can be defined in any cell type [24,43]; (v) SEs have a higher correlation with tumor-specific cell signaling pathways, such as the TGF-β and Wnt signaling pathways [44,45]; and (vi) SEs are more sensitive to external intervention, and the expression levels of SE-associated genes are more susceptible to transcriptional interference [46–48]. These observations indicate that SEs can be used as biomarkers to categorize cell types by comparing to typical enhancers. In summary, SEs and typical enhancers are similar in terms of structural composition, but their internal arrangement of TFs and cofactors as well as their binding density are different [13,36]. As a result, SEs perform a different function than typical enhancers. However, to understand whether SEs are fundamentally different from typical enhancers still requires further study. However, no set of rules can fully define all the characteristics of SEs because they are present in different cell types with different composition and properties. At present, it is feasible to identify SE regulatory regions of core genes that determine cell fate. More studies are required to explore these regulatory areas to better understand the characteristics of SEs. Although our studies on SEs have made some progress, they have also discovered new problems that need to be addressed. Due to the exceptional transcriptional activity of SEs, it is necessary for SEs to precisely bind to their target genes to prevent them from mistakenly driving adjacent genes unrelated to tumor function.

2.3. Identification of SEs

In previous studies, Richard A. Young and colleagues compared the

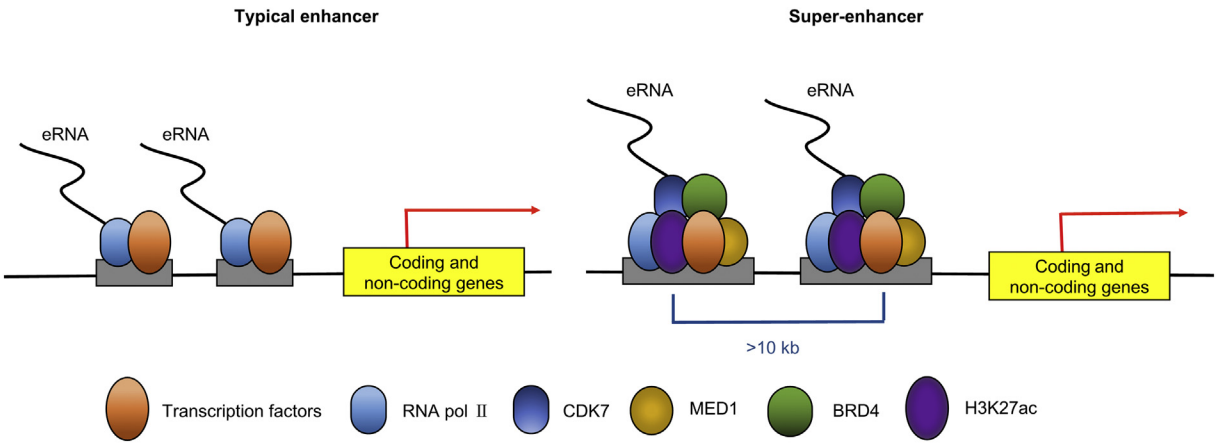

Fig. 1. Comparison of Super-enhancers and typical enhancers. In contrast to typical enhancers, Super-enhancers comprise large clusters of enhancer that are densely occupied with H3K27ac, CDK7, BRD4, MED1, and lineage-specific or master transcription factors.

relative ability of chromatin-immunoprecipitation sequencing (ChIP-Seq) data to H3K27ac, H3K4me1, mediator, and DNase I hypersensitivity data to distinguish SEs from typical enhancers. In this identification process, the enrichment of these enhancer transcription activity marker molecules on the genome was first analyzed by ChIP-Seq to determine the activity enhancer site. Within the genome, if these single enhancer entities were within the 12.5 kb range, they were merged into a single entity, the stitched enhancer. The stitched enhancer and the remaining individual enhancers were sorted according to the signal strength of the labeled molecules measured by ChIP-seq and plotted into a graph. The signal value of the marker molecule at the tangent point of the tangent line with a slope of 1 on this curve was the dividing line, in which molecules higher than this value were considered as SEs with the remaining considered as typical enhancers. Finally, these authors found that mediator was the most effective sign in distinguishing SEs from typical enhancers [29]. Previous studies have also confirmed that the domains of SEs are occupied by various histone modifiers, chromatin regulators, RNA Pol II, TFs and cofactors [41]. Khan et al. found that H3K27ac, p300, cyclin-dependent kinase 7 (CDK7), cyclin-dependent kinase 9 (CDK9), and mediator complex subunit 1 (MED1) as the six most important factors by ranking chromatin features [49]. Of note, H3K27ac and bromodomain-containing protein 4 (BRD4) perform optimally and each could be used to some degree to distinguish SEs from typical enhancers. However, the use of ChIP-seq data to distinguish the occupancy of different factors in SEs has not yet been well characterized. Previous studies have only shown that these highly ranked factors mediate gene transcription.

H3K27ac is a modification on the DNA-packaging protein, histone H3 [50]. Currently, H3K27ac is the most frequently used marker for identifying SEs [51]. Due to the high reliability of H3K27ac ChIP-seq data in SEs, the combination of Rank Ordering of Super-Enhancer (ROSE) with the activity of molecular H3K27ac has been widely used to distinguish SEs from typical enhancers [13].

BRD4, a member of the bromodomain and extraterminal domain (BET) protein family, is the second strongest marker for SEs in various cell types. BRD4 is a transcriptional regulator and epigenetic reader in cells that can bind to acetylated lysine in histones [52]. BRD4 induces the expression of cell type-specific genes by preferentially binding active enhancers. The main mechanism of BRD4 is to promote phosphorylation of RNA Pol II and then mediate transcriptional elongation of target genes [53,54]. Furthermore, BRD4 is also related to anti-suspension enhancers that regulate the proximal suspension release of RNA Pol II promoters [55].

Recently, increasing studies on SEs have highlighted the other two key factors, namely, CDK7 and MED1. CDK7, identified as a member of the cyclin-dependent kinase family, regulates transcription initiation by promoting phosphorylation of RNA Pol II. Thus, CDK7 is considered a key component of the transcription apparatus [56].

MED1, which is one of the critical components of the large multiprotein complex, acts as a key player in the transcription of RNA Pol II by binding DNA to the regulatory signals of gene-specific TFs [57]. Moreover, MED1 contributes to the formation of enhancer-promoter looping and three-dimensional (3D) genome organization [58]. Additionally, MED1 plays a major coordinating role in cell lineage and development [59].

To summarize, the combination of ROSE with the activity of molecular H3K27ac as analyzed by ChIP-Seq can identify SEs. In addition, several cofactors (MED1), chromatin regulators (BRD4), and signaling factors (CDK7) can also be used for SE identification [60,61]. However, the other master TFs that form the SE domain are still unclear. Previous studies have only indicated the possibility that multiple cofactors play a pivotal role in SE formation. To the best of our knowledge, there are three SE databases, including dbSUPER [62], SEA [60], and SEdb [63], which gather published SEs and implement the ROSE algorithm to mine available ChIP-seq data.

2.4. Biological function of SEs

SEs are enhancer clusters with cell type specificity that define identity and biological function by driving the expression of key cell identity genes [64]. SEs not only determine the identity of cells but also have the ability to maintain the characteristic of cancer cells and distinguish cancer subtypes [65]. Multiple SEs can promote gene regulation via several methods through specific loci with differences in activation during the developmental stage or synergetic gene expression. Additionally, somatic mutations frequently related to cancer often occur in SE-enriched genomes and are directed by SEs [66,67]. A phenomenon called "enhancer hijacking" has been reported by several studies on the mechanism of tumorigenesis. This phenomenon describes SEs as multi-component regulatory elements that can drive the expression of oncogenes in different cellular environments [68]. For example, a study on adenoid cystic carcinoma found that SE translocation drives the overexpression of oncogenic TFs in cancer cells [69]. Translocated SE elements shelter TF-binding sites, rendering TFs active, resulting in a positive feedback loop, further strengthening TF expression [70]. Another example of enhancer hijackings has been reported in acute myeloid leukemia (AML) with the translocation of SEs in the locus leading to the reorientation of the original tumor suppressor genes into oncogenes, ultimately promoting the occurrence of tumors [71,72]. Previous research has shown that SEs have a pivotal role in cell development and determine cellular identity [73]. A recent study has found that SEs play a general role in the genome of cells in addition to playing a regulatory role in different cell types [12]. However, the role of SEs in genome regulation is not fully elucidated.

Previous classical transcriptional control models have provided important insights into SE regulatory principles. Recently, a phase separation model has been proposed in the study of SEs [37]. High-density aggregates of polyvalent molecules and nucleic acids as well as their synergistic interactions result in the formation of phase separation [74]. In cell biology, phase separation refers to a specific state of intracellular aggregation of biological macromolecules [37,75], and it is similar to the process by which the liquid and solid of a substance change into each other in physical chemistry. The phase separation process plays an important role in 3D genomic tissue and participates in the identification of tissue cell identity [76]. Richard Young's group reported that the transcriptional coactivators, BRD4 and MED1, promote the phase separation process by forming a liquid–liquid phase separation (LLPS) around the SE domain. This process gathers the transcription machinery near the SEs to achieve the compartmentalization response of the transcription process. Intrinsically disordered regions (IDRs) play a key role in the phase separation process [77]. This kind of regulation mechanism is particularly suited to assembly and activation of SEs. Compared to typical enhancers, the formation of phase-separated multimolecular assemblies may occur more frequently during SE formation. Therefore, SEs contribute more to transcriptional regulation than the additive effect of their multiple components. As described above, SEs are considered a collaborative assembly of high-density TFs, chromatin regulators, transcription cofactors, and RNA Pol II [40] (Fig. 2). Thus, SEs can drive higher levels of transcription than typical enhancers and are particularly sensitive to interference with enhancer-related components. This model provides a profound insight into the formation, disturbance resistance and co-activation of multiple genes of SEs. Additionally, a similar study has proposed that SEs have potential functions in remote chromatin communication and the establishment of 3D chromatin rings [78]. The biological functions of SEs have been studied by many researchers, which has also provided insights into the understanding of SEs. However, little is known about the potential mechanism of SEs in specific cells. Therefore, focusing on the regulatory mechanism of SEs is still a future research direction.

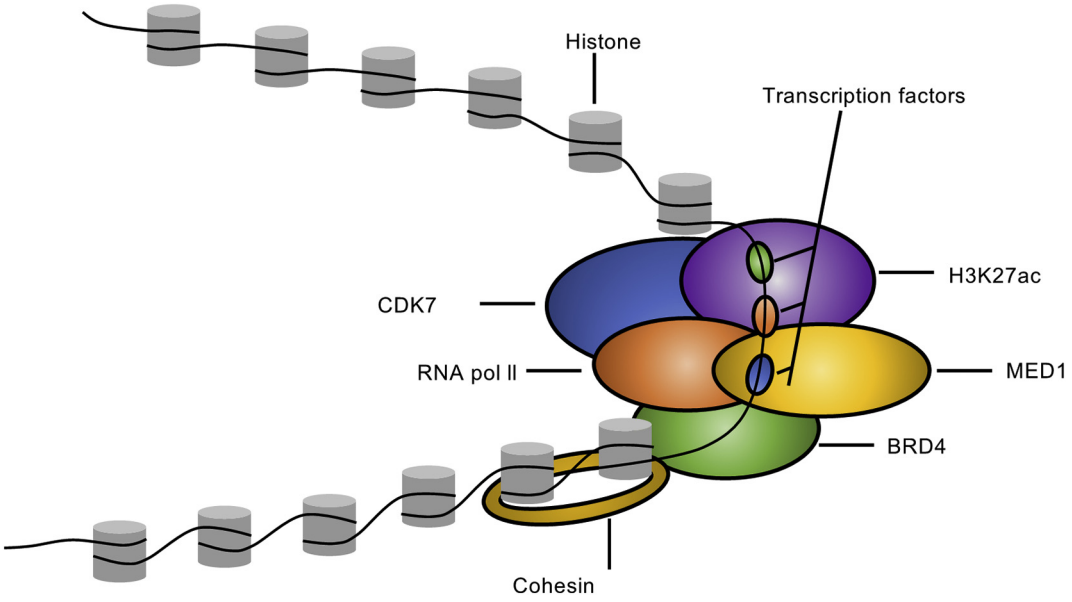

Fig. 2. Super-enhancer region combines multiple transcription factors to regulate gene transcription status.

2.5. SEs in tumors

As is well-known, gene transcription regulation governs the type of cell differentiation and the fate of organ development. Cancer is driven by transcriptional dysregulation of proto-oncogene and tumor-suppressive pathways. Thus, transcriptional dysregulation mediated by epigenetic or genetic alterations often results in the formation of cancer. Abnormal transcription of genes driven by SEs is essential for maintaining the characteristics of tumor cells. By assembling their own SEs, tumor cells can significantly promote the expression of a variety of oncogenes, thereby enhancing the biological function of tumor cells [79]. Compared to promoters and typical enhancers, a larger spectrum of cancer-associated mutations is found in SEs. In some tumors, small mutations and indels can randomly generate new SEs that can drive oncogenes of tumor pathogens [80]. Increasing evidence suggests that SEs are involved in the development of several tumors and maintain the characteristics of tumor cells. Therefore, SEs may be a potential biomarker in tumor cells [19,24,26,52,53]. Compared to their normal counterparts, tumor cells have altered SE usage and expression patterns [81]. Accordingly, SEs are enriched in genes and non-coding RNAs, known as oncogenic function, in tumor cells. Although SEs are specific to different tumor types, they could regulate the expression of the same genes in different tumors [34]. For example, Loven et al. reported that SEs are highly enriched in the MYC locus and overlap in different types of tumors [15]. Futhermore, MYC acquires large SEs that are tumour type-specific and absent from the normal cells [13]. In squamous cell carcinoma (SCC), CCAT1 has been identified as a new SE-associated oncogenic lncRNA [82]. As newly developed regulators, numerous studies have identified SEs in diverse tumors and shown that SEs promote the malignant phenotype of tumor cells. In summary, these results indicate that SEs contribute to tumor development by strongly enriching and driving tumor-specific genes and non-coding RNAs.

2.6. SEs in glioma

Transcription dysregulation is regulated by epigenetic and genetic alterations targeting non-coding regulatory elements. These effects can lead to the occurrence and development of tumors. SE involvement in the occurrence and development of glioma has been reported [16,17,83,84]. By using the CHIP-seq analysis of H3K27ac and MED1, many SE-associated genes, including WNT7B, FOSL1, FOXL2, and ZMIZ1, have been identified in glioma cells. Individual silencing of these genes significantly impairs the proliferation of glioma cells [16]. A separate study on diffuse intrinsic pontine glioma (DIPG) has shown that numerous genes related to SEs are markers of the state of undifferentiated nerve cells. Furthermore, a set of SE-associated genes mediates the identity and malignant state of DIPG cells [17]. In another similar study, the researchers found that SE-related genes have important roles for glioblastoma (GBM) growth. In addition, SE inhibitors lead to considerable disruption of global gene transcription in GBM cells, preferentially targeting genes associated with SEs [84]. These results emphasize the essential role of SEs in glioma development. Thus, targeting SE-associated transcription addiction may be an effective therapeutic strategy against glioma. In this review, we will explore the role of SEs in driving protein-coding genes and non-coding genes, such as miRNA and lncRNA, in glioma as well as their mechanism for regulating the biological functions of glioma cells.

3. Protein-coding genes associated with SEs in glioma

Protein-coding genes involved in tumorigenesis have been well studied. Dysregulated gene expression mediated by transcriptional regulation promotes malignant cell proliferation and eventually leads to tumors, suggesting that the dysregulation of transcription is an important oncogenic mechanism [85,86]. Studies have reported genes that play a pivotal role in glioma, and some of these genes are regulated by SEs in the progression of glioma (Table 1). Therefore, identification of novel SE-associated molecular markers targeting glioma and understanding their molecular mechanisms are critical for the treatment of glioma.

3.1. Cluster of differentiation 47 (CD47)

CD47, which is a cell surface glycoprotein, inhibits phagocytosis by binding to the extracellular region of SIRPa on macrophages [87]. In addition, CD47 is overexpressed in all types of human tumors [88]. Betancur et al. analyzed the CD47 regulatory genome to locate CD47 distal cis-regulatory regions (enhancers or SEs), and they also analyzed H3K27ac ChIP-Seq data and found that CD47 is regulated by different sets of SEs in different tumor cell types, such as T-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma [89]. Betancur et al. also discovered that CD47-associated SEs link TNF-NFKB1 signaling to

Table 1
Protein-coding genes regulated by SEs in glioma

Gene family	Relstive expression in glioma	Cell biology	Tumors	Diseases in SEs	Identification of SEs	Refs
CD47	Up-regulation	Proliferation	Glioma, pancreatic cancer, lung cancer, hepatocellular carcinoma	Pro-inflammatory in breast cancer	ChIp-seq (H3K27ac, H3K4me1)	[87–92]
MYC	Up-regulation	Proliferation, migration, invasion	Glioma, small lung cancer, neuroblatoma tumour, breast cancer, colorectal cancer	Osteocarcoma	ChIp-seq (H3k27ac, MYC)	[93–99]
EFGR	Up-regulation	Invasion, angiogenesis	Glioma, breast cancer, lung cancer, bladdercancer, prostaticancer, cervical cancer	Human, Papillomaviruses(HPV) cancer	ChIp-seq (H3K23ac, H3K4me3, H3K4me1, KDM5C), RNA-seq	[102–107]
c-MET	Up-regulation	Aggressiveness, invasion	Glioma, cervical cancer, breast cancer, liver cancer	Human papillomaviruses(HPV) cancer	ChIp-seq (H3K23ac, H3K4me3, H3K4me1, KDM5C) RNA-seq	[109–113]
GATA2	Up-regulation	Proliferation, migration, invasion	Glioma, leukemia, prostatic cancer, non-small cell lung cancer	Huntington's disease (HD)	ChIp-seq (H3K23ac, RNAPII) RNA-seq	[114–117]
LDLR	Up-regulation	Proliferation	Glioblastoma, nasopharyngeal cancer, gastric cancer, small cell lung cancer	Nasopharyngeal cancer	ChIP-seq	[119–122]
PAK4	Up-regulation	Proliferation, migration, invasion	Oesphageal squamous cell carcinoma, breast cancer, colon cancer, prostatic cancer	Oesphageal squamous cell carcinoma	ChIp-seq (H3K23ac)	[124–129]

CD47 upregulation in breast cancer [89]. These results suggest that SEs affect the malignancy of tumors by upregulating the expression of CDK7 in different tumor types. It has been demonstrated that high expression of CD47 is associated with a high degree of malignancy and invasiveness in glioma [90]. Additionally, glioma cells highly enriched with CD47 have stem progenitor cell-like characteristics, and silencing CD47 in glioma results in a decrease in these characteristics [91]. A similar study has shown that knockdown of CD47 inhibits tumor growth in pediatric brain tumor models [92]. These results indicate that SEs may enhance the malignancy of glioma cells by driving the expression of CD47. Therefore, the blockade of CD47 associated with SEs may be a novel therapeutic option to target glioma stem cells.

3.2. Oncogene c-MYC (MYC)

MYC, known as a transcription factor of the helix-loop-helix-leucine zipper (HLH-LZ) family, binds DNA as part of several protein complexes [93]. A broad body of evidence has established that dysregulated MYC expression promotes the development of a variety of tumors and creates a favorable environment for the survival of tumor cells in vivo [94,95]. It has been demonstrated that most SE genes associated with osteosarcoma bind to MYC. In addition, the treatment of osteosarcoma cells with SE inhibitors effectively inhibits the malignant phenotype of osteosarcoma cells [96]. These results demonstrate that SE signaling driven by MYC is critical for the biological function of osteosarcoma cells. Another study has shown that MYC regulates transcriptional amplification by SEs, which is a main hallmark of cancer [97]. Recent studies have shown that MYC overexpression is positively correlated with glioma grade and that increased MYC level is observed in approximately 60-80% gliomas [98]. Inhibition of MYC represses the proliferation of tumor cells, damages cell activity, and promotes apoptosis [99]. Additionally, several studies have proposed that MYC overexpression plays a central role in glioma progression driven by a variety of different mutations [100,101]. Therefore, these studies suggest that the inhibition of MYC associated with SEs may be an effective treatment strategy for glioma.

3.3. Epidermal growth factor receptor (EGFR)

EGFR is a member of the ERBB transmembrane tyrosine kinase receptor family [102]. EGFR overexpression promotes tumor cell proliferation, invasion, and angiogenesis but impedes apoptosis [103,104]. Chen et al. showed that SEs promote the proliferation, migration, and invasion of tumor cells by driving EGFR overexpression [105]. It has been demonstrated the high expression of EGFR is related to a variety of human tumors including GBM [106]. The upregulation of EGFR is associated with poor prognosis in patients with glioma [107]. Furthermore, upregulated EGFR promotes the malignant phenotype of tumors via receptor phosphorylation and downstream signaling pathway activation [108]. As the new research field of glioma is rapidly expanding, SE-driven EGFR may become a major focus for targeted cancer therapy for glioma.

3.4. Mesenchymal-epithelial transition factor (c-MET)

c-Met, known as a transmembrane receptor tyrosine kinase, consists of α- and β-chains linked by disulfide bonds. c-Met is activated by hepatocyte growth factor (HGF) and promotes tumor cell progression and metastasis [109]. Overexpression of c-Met is correlated with poor prognosis of patients with tumors [110]. A recent study from Chen et al. showed that epigenetic activation of SEs in the genome drives the expression of key oncogenes such as c-Met [105]. A recent study has reported that c-Met overexpression occurs in GBM and that c-Met gene amplification promotes malignancy [111]. A similar study has shown that c-Met amplification is partially associated with the aggressiveness of glioma [112]. More importantly, the upregulation of c-Met is related

Table 2
MiRNAs regulated by SEs in glioma

MiRNA famliy	Relstive expresion in glioma	Cell biology	Tumors	Target genes	Identification of SEs	Refs
miR-155	Up-regulation	Proliferation, migration, invasion	Glioma, colorectal cancer, diffuse large B-cell lymphoma	CDX1	ChIP-seq (BRD4, P65, RNA pol II)	[137–141]
miR-21	Up-regulation	Proliferation	Glioma, breast cancer, colon cancer, pancreatic cancer	SPRY1, P53, AKT, IGFBP3	ChIP-seq (H4K27ac)	[144–148]
miR-17	Up-regulation	Proliferation	Glioma, neuroblastoma, lung cancer, colon cancer	MYC, E2F1-3, Rbl2, Pten	ChIP-seq (H3K4 me3)	[149–152]

to shorter survival and poor therapeutic response for glioma [113]. Therefore, these studies suggest that c-Met driven by SEs may promote malignancy and be associated with poor clinical outcome in glioma.

3.5. GATA binding protein 2 (GATA2)

GATA proteins are TFs with central roles in early embryonic development and lineage specification [114]. GATA2, a member of the GATA protein family, is a major regulator of hematopoietic function, which involves the initial formation and maintenance of hematopoietic stem cells (HSCs) [115]. After translocation, the GATA2 enhancer region acquires the characteristics of SEs in the MOLM-1 genome [15]. A present study revealed that striatal SEs display extensive H3K27 acetylation within gene bodies and are enriched in binding motifs for GATA2 TFs [116]. Wang et al. demonstrated that high expression of GATA2 is positively related to the malignant degree of glioma. GATA2 overexpression promotes the malignant phenotype of glioma [117]. Another study has shown that GATA2 controls the expression of tumor-related blood vessels in glioblastoma and promotes angiogenesis [118]. Therefore, these results indicate that SEs may mediate the malignant phenotype of glioma cells via GATA2.

3.6. Low-density lipoprotein receptor (LDLR)

LDLR is an integral membrane protein that is abundantly expressed in the liver [119]. The characterization of SE-mediated networks in nasopharyngeal cancer has identified many novel SE-associated oncogenic transcripts, such as LDLR [120]. LDLR is highly upregulated in a variety of tumors. LDLR is also expressed in normal brain tissue and has a dual-targeting effect on the blood-brain barrier and glioma cells, making it a potential target receptor for the brain tumor drug delivery system [121,122]. Another study has shown that targeting LDLR in GBM inhibits the growth of tumor cells, thereby playing an anti-tumor role [123]. These results suggest that LDLR associated with SEs can affect the progress of glioma.

3.7. p21-activated kinases 4 (PAK4))

PAK4 is a Cdc42 effector protein that is involved in key functions in embryos, neurons, and immune defense [124]. PAK4 regulates the biological function of tumor cells dependent on actin cytoskeleton [125]. Recently, a comprehensive analysis of both SE-associated and THZ1-sensitive transcripts identified several novel esophageal squamous cell carcinoma (OSCC) oncogenes, including PAK4 [126]. A broad body of evidence has established that PAK4 is overexpressed in several types of tumors and promotes the growth of tumor cells [127,128]. Kesanakurti et al. demonstrated that PAK4 is aberrantly expressed in glioma and that PAK4 knockdown decreases migration and invasion of glioma cells [129,130]. In addition, overexpression of PAK4 promotes mesenchymal transformation by upregulating Epithelial-mesenchymal transition(EMT)markers in glioma cells [131]. Therefore, these results suggest that PAK4 associated with SEs may regulate the invasion and EMT of glioma cells.

4. miRNAs associated with SEs in glioma

MiRNAs are a class of endogenous small (19-25 nucleotides) non-coding single-stranded RNAs that are involved in post-transcriptional regulation either by degrading specific RNAs or inhibiting translation [132]. The role of miRNAs in gene transcriptional regulation and cell biological function has been elucidated in many different types of tumors. As a key regulatory factor of gene expression, miRNAs play a role in proliferation, differentiation, and apoptosis. Increasing evidence suggests that dysregulated miRNAs are related to the development of tumors [133]. MiRNAs can serve as tumor suppressors or oncogenes to influence tumor progression by regulating the malignant phenotype of

Table 3
LncRNAs regulated by SEs in glioma

LncRNA family	Relstive expresion in glioma	Cell biology	Tumors	Target gene	Identification of SEs	Refs
CCAT1	Up-regulation	Proliferation, migration, invasion	Glioma, colon cancer, gastric cancer, gallbladder cancer	miR-410, miR-18b	ChIP-seq (H3K27ac), RNA-seq	[82,162–164]
Linc00152	Up-regulation	Proliferation, migration, invasion	Glioma, hepatocellular carcinoma, gallbladder cancer, lung adenocarinoma	miR-16, miR-103a-3p	ChIP-seq (TF), CRISPR/Cas9 target sites, Rank Ordering of Super-enhancer (ROSE)	[60,166–170]
NEAT1	Up-regulation	Proliferation	Glioma, kideny cancer, lung caner, ovarian cancer	miR-449-5p, miR-181b-5p, miR-132, miR-410	ChIP-seq (H3K27ac, H3K4me1, H3K4me3)	[172–175]

glioma cells [134–136]. Recently, several studies have found that miRNAs associated with SEs play a central role in glioma (Table 2).

4.1. miR-155

MiR-155, located on chromosome 21, is an oncogenic miRNA [137]. As a multifunctional miRNA, miR-155 plays a crucial role in a variety of physiological and pathological processes of cells. Increasing evidence suggests that miR-155 is highly expressed in many different types of tumors [138–140]. Duan et al. revealed that SEs at miR-155 target genes regulated by NF-κB and BET drive miR-155 transcription-mediated self-regulation of inflammation [141]. Sun et al. showed that upregulated miR-155 is positively correlated with the pathological grade of gliomas and that high miR-155 expression indicates a low survival rate of patients [142]. In addition, miR-155 promotes glioma progression and increases malignancy by enhancing the Wnt signaling pathway [143]. Therefore, these findings indicate that miR-155 driven by SEs may promote malignant phenotype of glioma.

4.2. miR-21

MiR-21, one of the most studied miRNAs, has been shown to be highly expressed in various types of tumors, promoting tumor progression and serving as a biomarker for tumor prognosis [144]. A previous study has reported that SEs contribute to the progression of certain tumor types by enhancing the expression of miRNAs, such as miR-21 [145]. Yang et al. reported that the upregulation of miR-21 is inversely associated with patient survival [146]. In addition, miR-21 affects molecular pathways, including RECK, insulin-like growth factor binding protein-3, and TIMP3 in glioma cells [147]. Recent studies have also demonstrated that miR-21 overexpression inhibits apoptosis and senescence of glioma cells by inhibiting the expression of PTEN, caspase-3, and caspase-9 as well as by promoting the expression of AKT, PI3K, P-AKT, and P53 [148]. These data indicate that miR-21 associated with SEs may promote the malignant phenotype of glioma by multiple signaling pathways.

4.3. miR-17

MiR-17 belongs to the miR-17/92 cluster, which is abundantly expressed during neuronal and embryonic development [149]. The oncogenic activity potential of miR-17 gene clusters was initially identified in mouse viral tumors [150]. The activating mutations of miR-17 have been observed in different types of tumors [151]. A recent ChIP-seq data analysis found that the locus of miR-17 is enriched with SEs. Moreover, SEs promote the progression of tumors by enhancing miR-17 expression [145]. MiR-17 is upregulated in glioma, and inhibition of miR-17 significantly reduces the cell viability of glioma cells and stimulates cell apoptosis [152]. Another study has demonstrated that miR-17 is highly expressed in human glioma samples and is correlated with the malignancy degree and prognosis [153]. Therefore, these studies suggest that miR-17 associated with SEs may be a potential therapeutic target of glioma.

5. LncRNAs associated with SEs in glioma

LncRNAs are RNAs longer than 200 nucleotides, and they do not have protein-coding ability [154]. LncRNAs may play a regulatory role in gene expression by serving as signal molecules, decoy molecules, guiding molecules and scaffold molecules [155]. Increasing evidence has shown that the dysregulation of lncRNAs is involved in the biological function of cells, leading to the development of tumors [156]. Additionally, lncRNAs have been correlated with invasion and metastasis in human cancers [157–159]. Several studies have shown that lncRNAs act as oncogenes, tumor suppressors or both, depending on the environment in which tumor cells are located. Recently, we found that

Table 4
Therapeutic targeting of SE-driven transcription in cancer

Transcriptional regulators	Inhibitors	The application in cancer	Effect on SE-driven transcription	Effects of SE inhibition on tumor biology	Refs
BRD4	JQ1, iBET, SF1126, MK-8628	AML, breast cancer, multiple myeloma	Inhibited binding of BET bromodomains to acetyllysines	Inhibited transcription of genes that sustain the aberrant growth and self-renewal properties	[181–188]
CDK7	THZ1, THZ2, LDC4297, BS-181	DIPG, multiple myeloma, melanoma, NPC, OCSS, cervical cancer	Abrogated phosphorylation of RNA pol II CTD at Ser-5 and Ser-7	Decreased tumor cells viability and invasion	[18,188–193]
CDK9	THAL-SNS-032, PHA-767491, CDKI-73	ALL, AML, colon cancer, cervical cancer	Blocked the phosphorylation of the transcriptional elongation factor P-TEFb on the C-terminal region of RNA Poly-II	Reduced in disease progression, tumor volume and promoted apoptosis	[49,190–192]
CDK12	THZ531	T-ALL, ewing sarcoma, breast cancer, ovarian cancers	Downregulation of DNA damage response and SE-associated genes	Promoted tumor cells apoptosis	[190–192]

several lncRNAs, including HOTAIR, MEG3, and lncRNA-ATB, are involved in the progression of glioma [160,161]. Moreover, several studies have found that lncRNAs associated with SEs may be a crucial regulator in glioma (Table 3).

5.1. Colon cancer-associated transcript 1 (CCAT1)

CCAT1, located at chromosome 8q24.21, is an ~2 kb lncRNA that was first found to be upregulated in colon cancer [162]. Xiang et al. found that CCAT1 regulated the CTCF protein to preserve chromatin cyclization between MYC enhancers and was enriched in the SE region of tumor cells [163]. A recent epigenomic analysis of SEs in squamous cell carcinoma (SCC) showed that TP63 and SOX2 co-bind to SE regions of CCAT1 [82]. Notably, CCAT1 has been found to be implicated in the pathogenesis of several types of tumors. Wang et al. demonstrated that CCAT1 expression is significantly upregulated in glioma and that CCAT1 knockdown represses cell vitality and colony formation ability in glioma [164]. Another study has reported that the upregulation of CCAT1 is related to the pathological grade and prognosis of patients with glioma [165]. Therefore, these results suggest that SE driven-lncRNA CCAT1 may be involved in the development of glioma.

5.2. Long noncoding RNA 00152 (Linc00152)

Linc00152, located on chromosome 2p11.2, is a recently identified tumor-promoting long non-coding RNA [166]. A pan-cancer study has demonstrated that linc00152 expression is regulated by SEs and is strongly enriched in the SE region [60]. Wei et al. investigated the relationship between linc00152 and SEs by using the SEA database, and they suggested that linc00152 is driven by SEs [60]. Increasing evidence suggests that the aberrant expression of linc00152 contributes to the malignancy of cancers [167–169]. Chen et al. showed that linc00152 is highly expressed in glioma cells and enhances the proliferation, migration, and invasion, and they also reported that knockdown of linc00152 inhibits growth and increases apoptosis in glioma [170,171]. Therefore, these findings indicate that linc00152 associated with SEs may promote the malignant phenotype of glioma.

5.3. Nuclear paraspeckle assembly transcript 1 (NEAT1)

NEAT1 is a nuclear-enriched lncRNA that is necessary for the formation of nuclear paraspeckles [172]. A recent integrative analysis using both whole-transcriptome sequencing (RNA-Seq) and ChIP-Seq characterization of SE-mediated networks has identified many novel SE-associated oncogenic transcripts, including NEAT1, in nasopharyngeal carcinoma (NPC) [173,174]. It has been demonstrated that high expression of NEAT1 is positively correlated with the pathological grade of glioma [175]. However, knockdown of NEAT1 inhibits the malignant phenotype of glioma cells [156]. Chen et al. found that NEAT1 enhances the malignancy of glioma by activating the WNT/beta-catenin pathway [176]. Therefore, these studies suggest that NEAT1 mediated by SEs may promote the malignant phenotype of glioma.

6. SEs inhibitors and their applications in glioma

We have discussed the biological functions of SE-driven protein-coding genes and non-coding genes (miRNAs and lncRNAs) in glioma. We observed that the abnormal transcription driven by SEs can regulate malignant biological behavior of cancer cells. Moreover, we believe that cancer cells may be highly dependent on these transcriptional programs, which generates new targets for therapeutic interventions of cancers. As the core regulatory factors of gene transcription, SE complexes play key roles in the process of oncogene transcription. Increasing studies have shown that the repression of oncogenes by inhibiting SE complexes has become the most attractive target in cancer

therapy [177,178]. Interestingly, some studies have shown that the same oncogenes can form different SE structures in different tumors types [79]. However, the components of SEs are the same in different tumor cells, which allows direct inhibition of the most common components of SEs to prevent oncogenes from becoming resistant to SEs. Currently, this approach has been used in a variety of cancer models, showing great potential. It is important to further identify the composition of SEs, which will allow more inhibitors targeting the key components of SEs to be applied in cancers in the future. There is evidence that targeting these core transcriptional networks, either by knockdown by RNA interference or small molecule inhibitors, may block cancer development [179,180].

Several new drugs targeting SE complexes have been recently found to affect cellular transcription mechanisms, resulting in anti-tumor effects (Table 4). Inhibitors of SE complexes, including BRD4 and CDKs, block transcription by inhibiting RNA polymerase II or affecting covalent modification of histones [65]. Treatment of cancer cells with these inhibitors may result in acute and simultaneous repression of multiple oncogenes, thereby leading to the destruction of various carcinogenic mechanisms.

The BET family is composed of four members (BRD2, BRD3, BRD4, and BRDT), which share a C-terminal extraterminal motif and two N-terminal tandem bromodomains [181]. The BET inhibitor (BETi) is a competitive inhibitor of the BET family bromine domain, which competitively inhibits the binding of the BET bromine domain to acetyllysine, thereby inhibiting the extension of transcription [182]. Among all of the family members, BRD4 is one of the most widely studied genes, and it plays a significant role in gene transcriptional regulation [183]. Therefore, the blockade of BET by inhibiting BRD4 is used in many studies. BRD4 inhibitors inhibit the recruitment of the positive transcriptional extension factor complex, resulting in gene transcription interruption [184]. At present, the following BRD4 inhibitors have been reported: JQ1, I-BET151, AZD5153, and MK-8628 [185,186]. A recent study has reported that JQ1 represses the transcription of oncogenes that sustain the aberrant growth and self-renewal properties in acute myeloid leukemia (AML) [187]. Additionally, JQ1 impairs the activity of DIPG cells by inhibiting SE-driven transcription [188].

Other studies have indicated that CDK7 inhibitors have become one of the powerful candidates to target oncogenic SEs [189]. CDK7 inhibitors include THZ1, THZ2, LDC4297, and BS-181 [190–192]. As a covalent inhibitor of CDK7, THZ1 inhibits transcription by eliminating CDK7-dependent phosphorylation of RNA Pol II CTD on Ser-5 and Ser-7 [193]. A recent study has reported that THZ1 treatment results in considerable disruption of global gene transcription in glioma cells, preferentially targeting SE-associated genes [18]. These studies suggest that targeting the CDK7-dysregulated transcription program with SE inhibitors may be an effective treatment strategy for glioma. Similarly, THZ1 inhibits the transcription of related oncogenes by inhibiting SEs, which ultimately results in the destruction of DIPG cell viability. Additionally, THZ1 treatment modestly increases survival in a patient-derived DIPG xenograft model [188]. However, further investigation is required to understand whether THZ1 has better brain penetration. In summary, drugs that inhibit CDK7 and BRD4, such as JQ1 and THZ1, respectively, specifically target the inhibition of SEs in tumors, providing an efficient way to treat tumors by only targeting tumor cells.

Increasing evidence suggests that SE inhibitors have great potential as selective, anti-cancer therapeutics. More studies are required to explore the mechanism of SE-driven oncogenic transcription addiction to identify new targets to block transcription to treat tumors. However, there are several problems associated with treating tumors by targeting SEs in tumor cells. As previously discussed, SEs are more sensitive to external signals than any other genomic region, and SEs control cell identity genes in both normal and diseased cells. Therefore, SE inhibitors must specifically target SEs in tumor cells without affecting SEs in normal cells, which is one of the most challenging issues in cancer treatment. Some researchers have found that most SEs are suppressed in cells, and only a small number of active SEs determine cell identity in different cells [71,194]. Compared to normal cells, tumor cells actively assemble SEs at oncogene domains to drive oncogene expression in the process of tumorigenesis [15]. These studies suggest that the strategy of targeting SEs is feasible in some tumors, which may provide novel therapeutic options for other malignant tumors that lack good drug therapies.

Because SEs are a series of enhancer clusters, they have some similar components as typical enhancers. Therefore, the use of SE inhibitors may inhibit typical enhancers in normal cells, resulting in transcriptional suppression and activation of new oncogenes. Thus, the non-specific targeting of general transcriptional machinery may also lead to cytotoxicity in non-malignant cells. Some researchers have addressed these challenges. Treatment of multiple myeloma tumor cells with JQ1 causes BRD4 to become imbalanced in the genome, and this imbalance is more frequent in the SE region than in the typical enhancer region [15]. This phenomenon is found in other tumors, such as B cell lymphoma and colorectal cancer [14,195]. Drugs, such as JQ1 and THZ1, specifically target the inhibition of SEs in tumors, providing an efficient way to treat tumors [15,193]. Additonally, recent studies have found that SE inhibitors (CDK7 inhibitors) are highly sensitive and specific to tumor cells [196,197]. Although SE inhibitors have been studied in many tumors, the potential side effects and off-target effects of SEs have not been fully investigated. Therefore, when SE inhibitors are used to treat tumors, their inhibitory effect on these tumors as well as their possible side effects should be studied to allow avoidance of these side effects in the future. Finally, these insights are important to understand the assembly and activation of SEs to identify more candidates that inhibit SEs in glioma (Fig. 3).

7. Conclusion and prospective

In this review, we summarized recent advances in the basic concepts, characteristics, and biological functions of SEs and their identification in different cells. In addition, we described the role of the protein-coding genes and non-coding genes (miRNAs and lncRNAs) driven by SEs in glioma. We also found that SEs are specific to the tumour type, but they can regulate the same gene in different tumours. Thus, it is clear that SEs have central effects on transcriptional regulation of glioma, and these SEs have oncogenic capability depending on the environment. However, the intrinsic properties of SEs and their interactions with target genes are still poorly understood. Moreover, the role of each SE complex component and how they work together to regulate gene expression require additional research and discussion. Future studies on SEs should focus on exploring the various components of SEs in different tumor cells and how they regulate the function of SEs and affect the biological function of tumor cells. The underlying mechanism of SEs in normal development and cancer conditions remains to be elucidated.

SE-related components of the glioma cell genome can be mapped using sequencing techniques followed by gene-editing techniques to knockout individual components to investigate their cooperative roles in SEs.

Because SE complexes are shared in diverse cancer subtypes, targeting individual components of SE complexes, such as BRD4 and CDK7, may have great potential in the treatment of cancers. In addition to applying genome-editing techniques, such as CRISPR/Cas9, for the analysis of SE components, this approach may also be a novel gene therapy to target oncogenic SEs. The characteristics of SEs in glioma provide a new framework for application of inhibitors that target SEs to destroy tumor cell transcription. However, challenges still exist. Although the role of SE inhibitors has been demonstrated in many tumor subtypes, the extent of their involvement remains controversial. Targeted SEs used in cancer treatment may cause significant side effects because some tumor suppressor genes may also be blocked by SE inhibitors. Therefore, before SEs can be used as a therapeutic target for

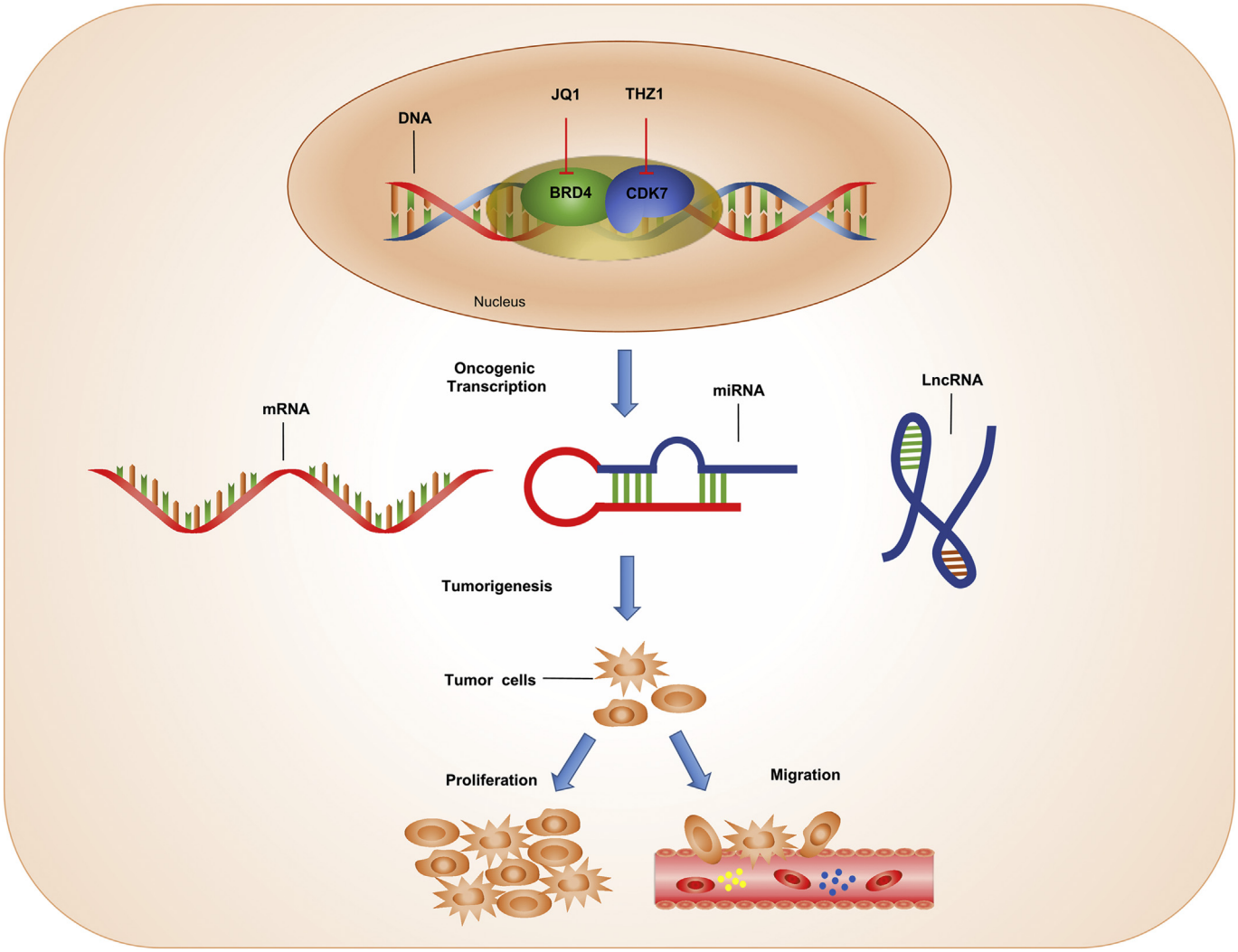

Fig. 3. Super-enhancer inhibitors block gene transcription by inhibiting the transcription factors of SE-complex.

glioma, there is an urgent need to better understand the mechanism of the addictive nature of SE-driven oncogene transcription.

High-throughput sequencing technology has revealed many SEs associated with tumors and other diseases. Despite the compelling evidence that SEs regulate cellular identity genes leading to tumors, there insufficient genetic evidence to determine whether individual SEs determine cell fate and change specific cell types. In this review, we emphasized that SEs play underappreciated but critical roles in glioma cells. SEs may increase the malignant degree of glioma cells by regulating the overexpression of protein-coding genes and non-coding genes. Therefore, we hypothesize that SEs may regulate the biological function of glioma cells by influencing SE-associated genes or non-coding RNAs. Moreover, SEs can be used as prognostic markers to predict the progression and risk of glioma. Integrative analysis of the SE signature and gene transcription profile of the glioma genome may be a novel approach for diagnosis. In corresponding fresh glioma samples and para-cancer tissue samples, the SE landscape can be established using ChIP-Seq technology to study the changes in the SE landscape in each stage of the occurrence and development of glioma. Finally, as the research field of SEs expands, increasing numbers of SEs associated with glioma will be found. In the future, SEs may be applied in clinical practice for the diagnosis, prognosis or treatment of glioma.

Abbreviations

SEs	Super-enhancers
TFs	Transcription factors
CDK7	Cyclin-dependent kinase 7
MED1	Mediator complex subunit 1
BRD4	Bromodomain-containing protein 4
BET	Bromodomain and Extraterminal domain
ROSE	Rank Ordering of Super-enhance
WHO	World health organization
GBM	Glioblastoma
ESC	Embryonic stem cells
ChIP-Seq	Chromatin-immunoprecipitation sequencing
AML	Acute myeloid leukemia
SCC	Squamous cell carcinoma
DIPG	Diffuse intrinsic pontine glioma
HSCs	Hematopoietic stem cells
OSCC	Oesophageal squamous cell carcinoma
BETi	BET inhibitor
EMT	Epithelial-mesenchymal transition
NPC	Nasopharyngeal carcinoma

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Authors' contributions

ZB and BEB conceived the idea presented,CM, JXH and ZZW collected relevant literature and drafted manuscripts, XYD modified and edited manuscripts, CM and BEB mapped these numbers, all authors have read and approved final manuscript.

Ethics approval and consent to participate

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Declaration of Competing Interest

The authors declare no conflict of interest.

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References

[1] Q.T. Ostrom, H. Gittleman, G. Truitt, A. Boscia, C. Kruchko, J.S. Barnholtz-Sloan, CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015, Neuro-Oncology 20 (suppl_4) (2018) iv1-iv86..
[2] D.N. Louis, A. Perry, G. Reifenberger, A. von Deimling, D. Figarella-Branger, W.K. Cavenee, H. Ohgaki, O.D. Wiestler, P. Kleihues, D.W. Ellison, The 2016 World Health Organization classification of tumors of the central nervous system: a summary, Acta Neuropathol. 131 (6) (2016) 803–820.
[3] A. Christians, A. Adel-Horowski, R. Banan, U. Lehmann, S. Bartels, F. Behling, A. Barrantes-Freer, C. Stadelmann, V. Rohde, F. Stockhammer, C. Hartmann, The prognostic role of IDH mutations in homogeneously treated patients with anaplastic astrocytomas and glioblastomas, Acta Neuropathol. Commun. 7 (1) (2019) 156.
[4] T.D. Bourne, D. Schiff, Update on molecular findings, management and outcome in low-grade gliomas, Nat. Rev. Neurol. 6 (12) (2010) 695–701.
[5] Natanael Zarco, Emily Norton, Alfredo Quiñones-Hinojosa, Hugo Guerrero-Cazares, Overlapping migratory mechanisms between neural progenitor cells and brain tumor stem cells, Cellular and molecular life sciences, CMLS 76 (18) (2019) 3553–3570.
[6] M. Erreni, G. Solinas, P. Brescia, D. Osti, F. Zunino, P. Colombo, A. Destro, M. Roncalli, A. Mantovani, R. Draghi, D. Levi, Y.B.R. Rodriguez, P. Gaetani, G. Pelicci, P. Allavena, Human glioblastoma tumours and neural cancer stem cells express the chemokine CX3CL1 and its receptor CX3CR1, Eur. J. Cancer 46 (18) (2010) 3383–3392.
[7] Y. Shi, Y.F. Ping, X. Zhang, X.W. Bian, Hostile takeover: glioma stem cells recruit TAMs to support tumor progression, Cell Stem Cell 16 (3) (2015) 219–220.
[8] A. Svensson, I. Ozen, G. Genove, G. Paul, J. Bengzon, Endogenous brain pericytes are widely activated and contribute to mouse glioma microvasculature, PLoS One 10 (4) (2015) e0123553.
[9] M.E. Davis, Glioblastoma: overview of disease and treatment, Clin. J. Oncol. Nurs. 20 (5 Suppl) (2016) S2–S8.
[10] F. Cheng, D. Guo, MET in glioma: signaling pathways and targeted therapies, J. Exp. Clin. Cancer Res. 38 (1) (2019) 270.
[11] P. Thandapani, Super-enhancers in cancer, Pharmacol. Ther. 199 (2019) 129–138.
[12] X. Wang, M.J. Cairns, J. Yan, Super-enhancers in transcriptional regulation and genome organization, Nucleic Acids Res. undefined(undefined) 47 (22) (2019) 11481–11496 undefined.
[13] D. Hnisz, B.J. Abraham, T.I. Lee, A. Lau, V. Saint-Andre, A.A. Sigova, H.A. Hoke, R.A. Young, Super-enhancers in the control of cell identity and disease, Cell 155 (4) (2013) 934–947.
[14] B. Chapuy, M.R. McKeown, C.Y. Lin, S. Monti, M.G. Roemer, J. Qi, P.B. Rahl, H.H. Sun, K.T. Yeda, J.G. Doench, E. Reichert, A.L. Kung, S.J. Rodig, R.A. Young, M.A. Shipp, J.E. Bradner, Discovery and characterization of super-enhancer-associated dependencies in diffuse large B cell lymphoma, Cancer Cell 24 (6) (2013) 777–790.
[15] J. Loven, H.A. Hoke, C.Y. Lin, A. Lau, D.A. Orlando, C.R. Vakoc, J.E. Bradner, T.I. Lee, R.A. Young, Selective inhibition of tumor oncogenes by disruption of super-enhancers, Cell 153 (2) (2013) 320–334.
[16] J. Lovén, H.A. Hoke, C.Y. Lin, A. Lau, D.A. Orlando, C.R. Vakoc, J.E. Bradner, T.I. Lee, R.A. Young, Selective inhibition of tumor oncogenes by disruption of super-enhancers, Cell 153 (2) (2013) 320–334.
[17] S. Nagaraja, N.A. Vitanza, P.J. Woo, K.R. Taylor, F. Liu, L. Zhang, M. Li, W. Meng, A. Ponnuswami, W. Sun, J. Ma, E. Hulleman, T. Swigut, J. Wysocka, Y. Tang, M. Monje, Transcriptional dependencies in diffuse intrinsic pontine glioma, Cancer Cell 31 (5) (2017) 635-652.e6.
[18] W. Meng, J. Wang, B. Wang, F. Liu, M. Li, Y. Zhao, C. Zhang, Q. Li, J. Chen, L. Zhang, Y. Tang, J. Ma, CDK7 inhibition is a novel therapeutic strategy against GBM both in vitro and in vivo, Cancer Manag. Res. 10 (2018) 5747–5758.
[19] M.S.Y. Tan, E. Sandanaraj, Y.K. Chong, S.W. Lim, L.W.H. Koh, W.H. Ng, N.S. Tan, P. Tan, B.T. Ang, C. Tang, A STAT3-based gene signature stratifies glioma patients for targeted therapy, Nat. Commun. 10 (1) (2019) 3601.
[20] L. Yu, J. Xu, J. Liu, H. Zhang, C. Sun, Q. Wang, C. Shi, X. Zhou, D. Hua, W. Luo, X. Bian, S. Yu, The novel chromatin architectural regulator SND1 promotes glioma proliferation and invasion and predicts the prognosis of patients, Neuro-oncology 21 (6) (2019) 742–754.
[21] Zixuan Peng, Changhong Liu, Minghua Wu, New insights into long noncoding RNAs and their roles in glioma, Mol. Cancer 17 (1) (2018) 61.
[22] R. Rynkeviciene, J. Simiene, E. Strainiene, V. Stankevicius, J. Usinskiene, E. Miseikyte Kaubriene, I. Meskinyte, J. Cicenas, K. Suziedelis, Non-coding RNAs in Glioma, Cancers (Basel) 11 (1) (2018).
[23] V. Bhaskaran, M.O. Nowicki, M. Idriss, M.A. Jimenez, G. Lugli, J.L. Hayes, A.B. Mahmoud, R.E. Zane, C. Passaro, K.L. Ligon, D. Haas-Kogan, A. Bronisz, J. Godlewski, S.E. Lawler, E.A. Chiocca, P. Peruzzi, The functional synergism of microRNA clustering provides therapeutically relevant epigenetic interference in glioblastoma, Nat. Commun. 10 (1) (2019) 442.
[24] S. Pott, J.D. Lieb, What are super-enhancers? Nat. Genet. 47 (1) (2015) 8–12.
[25] Ji-Han Xi, Gong-Hong Wei, Enhancer dysfunction in 3D genome and disease, Cells 8 (10) (2019) undefined.
[26] E. Smith, A. Shilatifard, Enhancer biology and enhanceropathies, Nat. Struct. Mol. Biol. 21 (3) (2014) 210–219.
[27] S.M. Glasgow, J.C. Carlson, W. Zhu, L.S. Chaboub, P. Kang, H.K. Lee, Y.M. Clovis, B.E. Lozzi, R.J. McEvilly, M.G. Rosenfeld, C.J. Creighton, S.K. Lee, C.A. Mohila, B. Deneen, Glia-specific enhancers and chromatin structure regulate NFIA expression and glioma tumorigenesis, Nat. Neurosci. 20 (11) (2017) 1520–1528.
[28] T.H. Huang, Wu ATH, T.S. Cheng, K.T. Lin, C.J. Lai, H.W. Hsieh, P.M. Chang, C.W. Wu, C.F. Huang, K.Y. Chen, In silico identification of thiostrepton as an inhibitor of cancer stem cell growth and an enhancer for chemotherapy in non-small-cell lung cancer, J. Cell. Mol. Med. 23 (12) (2019) 8184–8195.
[29] W.A. Whyte, D.A. Orlando, D. Hnisz, B.J. Abraham, C.Y. Lin, M.H. Kagey, P.B. Rahl, T.I. Lee, R.A. Young, Master transcription factors and mediator establish super-enhancers at key cell identity genes, Cell 153 (2) (2013) 307–319.
[30] N. Dukler, B. Gulko, Y.F. Huang, A. Siepel, Is a super-enhancer greater than the sum of its parts? Nat. Genet. 49 (1) (2016) 2–3.
[31] D. Hay, J.R. Hughes, C. Babbs, J.O.J. Davies, B.J. Graham, L. Hanssen, M.T. Kassouf, A.M. Marieke Oudelaar, J.A. Sharpe, M.C. Suciu, J. Telenius, R. Williams, C. Rode, P.S. Li, L.A. Pennacchio, J.A. Sloane-Stanley, H. Ayyub, S. Butler, T. Sauka-Spengler, R.J. Gibbons, A.J.H. Smith, W.G. Wood, D.R. Higgs, Genetic dissection of the alpha-globin super-enhancer in vivo, Nat. Genet. 48 (8) (2016) 895–903.
[32] J.Y. Ko, S. Oh, K.H. Yoo, Functional enhancers as master regulators of tissue-specific gene regulation and cancer development, Mol. Cell 40 (3) (2017) 169–177.
[33] M. Garbajs, P. Strojan, K. Surlan-Popovic, Prognostic role of diffusion weighted and dynamic contrast-enhanced MRI in loco-regionally advanced head and neck cancer treated with concomitant chemoradiotherapy, Radiol. Oncol. 53 (1) (2019) 39–48.
[34] I. Sur, J. Taipale, The role of enhancers in cancer, Nat. Rev. Cancer 16 (8) (2016) 483–493.
[35] J. Banerji, S. Rusconi, W. Schaffner, Expression of a beta-globin gene is enhanced by remote SV40 DNA sequences, Cell 27 (1981) 299–308.
[36] Y. Peng, Y. Zhang, Enhancer and super-enhancer: positive regulators in gene transcription, Anim. Model Exp. Med. 1 (3) (2018) 169–179.
[37] D. Hnisz, K. Shrinivas, R.A. Young, A.K. Chakraborty, P.A. Sharp, A phase separation model for transcriptional control, Cell 169 (1) (2017) 13–23.
[38] D. Hnisz, J. Schuijers, C.Y. Lin, A.S. Weintraub, B.J. Abraham, T.I. Lee, J.E. Bradner, R.A. Young, Convergence of developmental and oncogenic signaling pathways at transcriptional super-enhancers, Mol. Cell 58 (2) (2015) 362–370.
[39] Enhancers and super-enhancers have an equivalent regulatory role in embryonic stem cells through regulation of single or multiple genes, 27 (2) (2017) 246–258.
[40] B.R. Sabari, A. Dall'Agnese, A. Boija, I.A. Klein, E.L. Coffey, K. Shrinivas, B.J. Abraham, N.M. Hannett, A.V. Zamudio, J.C. Manteiga, C.H. Li, Y.E. Guo, D.S. Day, J. Schuijers, E. Vasile, S. Malik, D. Hnisz, T.I. Lee, I.I. Cisse, R.G. Roeder,

P.A. Sharp, A.K. Chakraborty, R.A. Young, Coactivator condensation at super-enhancers links phase separation and gene control, Science 361 (6400) (2018).
[41] Y. Jia, W.J. Chng, J. Zhou, Super-enhancers: critical roles and therapeutic targets in hematologic malignancies, J. Hematol. Oncol. 12 (1) (2019) 77.
[42] Ying Ying, Yejun Wang, Xiaoyan Huang, Yanmei Sun, Junbao Zhang, Meiqi Li, Junhui Zeng, Maolin Wang, Wenjun Xiao, Lan Zhong, Bo Xu, Lili Li, Qian Tao, Xiaomei Wang, Xing-sheng Shu, Oncogenic HOXB8 is driven by MYC-regulated super-enhancer and potentiates colorectal cancer invasiveness via BACH1, Oncogene undefined(undefined) 39 (5) (2020) 1004–1017 undefined.
[43] L. Ke, H. Zhou, C. Wang, G. Xiong, Y. Xiang, Y. Ling, A. Khabir, G.S. Tsao, Y. Zeng, M. Zeng, P. Busson, E. Kieff, X. Guo, B. Zhao, Nasopharyngeal carcinoma super-enhancer-driven ETV6 correlates with prognosis, Proc. Natl. Acad. Sci. U. S. A. 114 (36) (2017) 9683–9688.
[44] Super-enhancers facilitate gene regulation by signaling pathways, Cancer Discov. 5 (5) (2015) OF11.
[45] X. Zhu, T. Zhang, Y. Zhang, H. Chen, J. Shen, X. Jin, J. Wei, E. Zhang, M. Xiao, Y. Fan, R. Mao, G. Zhou, A super-enhancer controls TGF- β signaling in pancreatic cancer through downregulation of TGFBR2, Cell. Signal. undefined(undefined) 66 (2020) 109470.
[46] D. Gosselin, V.M. Link, C.E. Romanoski, G.J. Fonseca, D.Z. Eichenfield, N.J. Spann, J.D. Stender, H.B. Chun, H. Garner, F. Geissmann, C.K. Glass, Environment drives selection and function of enhancers controlling tissue-specific macrophage identities, Cell 159 (6) (2014) 1327–1340.
[47] J. Qian, Q. Wang, M. Dose, N. Pruett, K.R. Kieffer-Kwon, W. Resch, G. Liang, Z. Tang, E. Mathe, C. Benner, W. Dubois, S. Nelson, L. Vian, T.Y. Oliveira, M. Jankovic, O. Hakim, A. Gazumyan, R. Pavri, P. Awasthi, B. Song, G. Liu, L. Chen, S. Zhu, L. Feigenbaum, L. Staudt, C. Murre, Y. Ruan, D.F. Robbiani, Q. Pan-Hammarstrom, M.C. Nussenzweig, R. Casellas, B cell super-enhancers and regulatory clusters recruit AID tumorigenic activity, Cell 159 (7) (2014) 1524–1537.
[48] H.E. Pelish, B.B. Liau, I.I. Nitulescu, A. Tangpeerachaikul, Z.C. Poss, D.H. Da Silva, B.T. Caruso, A. Arefolov, O. Fadeyi, A.L. Christie, K. Du, D. Banka, E.V. Schneider, A. Jestel, G. Zou, C. Si, C.C. Ebmeier, R.T. Bronson, A.V. Krivtsov, A.G. Myers, N.E. Kohl, A.L. Kung, S.A. Armstrong, M.E. Lemieux, D.J. Taatjes, M.D. Shair, Mediator kinase inhibition further activates super-enhancer-associated genes in AML, Nature 526 (7572) (2015) 273–276.
[49] A. Khan, X. Zhang, Integrative modeling reveals key chromatin and sequence signatures predicting super-enhancers, Sci. Rep. 9 (1) (2019) 2877.
[50] G. Fan, Q. Zhang, Y. Wan, F. Lv, Y. Chen, Y. Ni, W. Zou, W. Zhang, H. Wang, Decreased levels of H3K9ac and H3K27ac in the promotor region of ovarian P450 aromatase mediated low estradiol synthesis in female offspring rats induced by prenatal nicotine exposure as well as in human granulosa cells after nicotine treatment, Food Chem. Toxicol. 128 (2019) 256–266.
[51] M.P. Creyghton, A.W. Cheng, G.G. Welstead, T. Kooistra, B.W. Carey, E.J. Steine, J. Hanna, M.A. Lodato, G.M. Frampton, P.A. Sharp, L.A. Boyer, R.A. Young, R. Jaenisch, Histone H3K27ac separates active from poised enhancers and predicts developmental state, Proc. Natl. Acad. Sci. U. S. A. 107 (50) (2010) 21931–21936.
[52] B. Donati, E. Lorenzini, A. Ciarrocchi, BRD4 and cancer: going beyond transcriptional regulation, Mol. Cancer 17 (1) (2018) 164.
[53] W. Zhang, C. Prakash, C. Sum, Y. Gong, Y. Li, J.J. Kwok, N. Thiessen, S. Pettersson, S.J. Jones, S. Knapp, H. Yang, K.C. Chin, Bromodomain-containing protein 4 (BRD4) regulates RNA polymerase II serine 2 phosphorylation in human CD4+ T cells, J. Biol. Chem. 287 (51) (2012) 43137–43155.
[54] F. Itzen, A.K. Greifenberg, C.A. Bosken, M. Geyer, Brd4 activates P-TEFb for RNA polymerase II CTD phosphorylation, Nucleic Acids Res. 42 (12) (2014) 7577–7590.
[55] W. Liu, Q. Ma, K. Wong, W. Li, K. Ohgi, J. Zhang, A. Aggarwal, M.G. Rosenfeld, Brd4 and JMJD6-associated anti-pause enhancers in regulation of transcriptional pause release, Cell 155 (7) (2013) 1581–1595.
[56] D. Eick, M. Geyer, The RNA polymerase II carboxy-terminal domain (CTD) code, Chem. Rev. 113 (11) (2013) 8456–8490.
[57] J. Soutourina, Transcription regulation by the Mediator complex, Nat. Rev. Mol. Cell Biol. 19 (4) (2018) 262–274.
[58] B.L. Allen, D.J. Taatjes, The Mediator complex: a central integrator of transcription, Nat. Rev. Mol. Cell Biol. 16 (3) (2015) 155–166.
[59] J.W. Yin, G. Wang, The Mediator complex: a master coordinator of transcription and cell lineage development, Development 141 (5) (2014) 977–987.
[60] Y. Wei, S. Zhang, S. Shang, B. Zhang, S. Li, X. Wang, F. Wang, J. Su, Q. Wu, H. Liu, Y. Zhang, SEA: a super-enhancer archive, Nucleic Acids Res. 44 (D1) (2016) D172–D179.
[61] J.E. Bradner, D. Hnisz, R.A. Young, Transcriptional addiction in cancer, Cell 168 (4) (2017) 629–643.
[62] A. Khan, X. Zhang, dbSUPER: a database of super-enhancers in mouse and human genome, Nucleic Acids Res. 44 (D1) (2016) D164–D171.
[63] Y. Jiang, F. Qian, X. Bai, Y. Liu, Q. Wang, B. Ai, X. Han, S. Shi, J. Zhang, X. Li, Z. Tang, Q. Pan, Y. Wang, F. Wang, C. Li, SEdb: a comprehensive human super-enhancer database, Nucleic Acids Res. 47 (D1) (2019) D235–D243.
[64] A. Gurumurthy, Y. Shen, E.M. Gunn, J. Bungert, Phase separation and transcription regulation: are super-enhancers and locus control regions primary sites of transcription complex assembly? BioEssays 41 (1) (2019) e1800164.
[65] S. Sengupta, R.E. George, Super-enhancer-driven transcriptional dependencies in cancer, Trends Cancer 3 (4) (2017) 269–281.
[66] M.T. Maurano, R. Humbert, E. Rynes, R.E. Thurman, E. Haugen, H. Wang, A.P. Reynolds, R. Sandstrom, H. Qu, J. Brody, A. Shafer, F. Neri, K. Lee, T. Kutyavin, S. Stehling-Sun, A.K. Johnson, T.K. Canfield, E. Giste, M. Diegel, D. Bates, R.S. Hansen, S. Neph, P.J. Sabo, S. Heimfeld, A. Raubitschek, S. Ziegler, C. Cotsapas, N. Sotoodehnia, I. Glass, S.R. Sunyaev, R. Kaul, J.A. Stamatoyannopoulos, Systematic localization of common disease-associated variation in regulatory DNA, Science 337 (6099) (2012) 1190–1195.
[67] M.A. Schaub, A.P. Boyle, A. Kundaje, S. Batzoglou, M. Snyder, Linking disease associations with regulatory information in the human genome, Genome Res. 22 (9) (2012) 1748–1759.
[68] P.H. Krijger, W. de Laat, Regulation of disease-associated gene expression in the 3D genome, Nat. Rev. Mol. Cell Biol. 17 (12) (2016) 771–782.
[69] Y. Drier, M.J. Cotton, K.E. Williamson, S.M. Gillespie, R.J. Ryan, M.J. Kluk, C.D. Carey, S.J. Rodig, L.M. Sholl, A.H. Afrogheh, W.C. Faquin, L. Queimado, J. Qi, M.J. Wick, A.K. El-Naggar, J.E. Bradner, C.A. Moskaluk, J.C. Aster, B. Knoechel, B.E. Bernstein, An oncogenic MYB feedback loop drives alternate cell fates in adenoid cystic carcinoma, Nat. Genet. 48 (3) (2016) 265–272.
[70] M.S. Joo, J.H. Koo, T.H. Kim, Y.S. Kim, S.G. Kim, LRH1-driven transcription factor circuitry for hepatocyte identity: Super-enhancer cistromic analysis, EBioMedicine 40 (2019) 488–503.
[71] S. Groschel, M.A. Sanders, R. Hoogenboezem, E. de Wit, B.A.M. Bouwman, C. Erpelinck, V.H.J. van der Velden, M. Havermans, R. Avellino, K. van Lom, E.J. Rombouts, M. van Duin, K. Dohner, H.B. Beverloo, J.E. Bradner, H. Dohner, B. Lowenberg, P.J.M. Valk, E.M.J. Bindels, W. de Laat, R. Delwel, A single oncogenic enhancer rearrangement causes concomitant EVI1 and GATA2 deregulation in leukemia, Cell 157 (2) (2014) 369–381.
[72] H. Yamazaki, M. Suzuki, A. Otsuki, R. Shimizu, E.H. Bresnick, J.D. Engel, M. Yamamoto, A remote GATA2 hematopoietic enhancer drives leukemogenesis in inv(3)(q21;q26) by activating EVI1 expression, Cancer Cell 25 (4) (2014) 415–427.
[73] R.C. Adam, H. Yang, S. Rockowitz, S.B. Larsen, M. Nikolova, D.S. Oristian, L. Polak, M. Kadaja, A. Asare, D. Zheng, E. Fuchs, Pioneer factors govern super-enhancer dynamics in stem cell plasticity and lineage choice, Nature 521 (7552) (2015) 366–370.
[74] L.P. Bergeron-Sandoval, N. Safaee, S.W. Michnick, Mechanisms and consequences of macromolecular phase separation, Cell 165 (5) (2016) 1067–1079.
[75] B.A. Gibson, L.K. Doolittle, M.W.G. Schneider, L.E. Jensen, N. Gamarra, L. Henry, D.W. Gerlich, S. Redding, M.K. Rosen, Organization of chromatin by intrinsic and regulated phase separation, Cell 179 (2) (2019) 470-484 e21.
[76] R. Stadhouders, G.J. Filion, T. Graf, Transcription factors and 3D genome conformation in cell-fate decisions, Nature 569 (7756) (2019) 345–354.
[77] A. Boija, I.A. Klein, B.R. Sabari, A. Dall' Agnese, E.L. Coffey, A.V. Zamudio, C.H. Li, K. Shrinivas, J.C. Manteiga, N.M. Hannett, B.J. Abraham, L.K. Afeyan, Y.E. Guo, J.K. Rimel, C.B. Fant, J. Schuijers, T.I. Lee, D.J. Taatjes, R.A. Young, Transcription factors activate genes through the phase-separation capacity of their activation domains, Cell 175 (7) (2018) 1842-1855.e16.
[78] S.S.P. Rao, S.C. Huang, B. Glenn St Hilaire, J.M. Engreitz, E.M. Perez, K.R. Kieffer-Kwon, A.L. Sanborn, S.E. Johnstone, G.D. Bascom, I.D. Bochkov, X. Huang, M.S. Shamim, J. Shin, D. Turner, Z. Ye, A.D. Omer, J.T. Robinson, T. Schlick, B.E. Bernstein, R. Casellas, E.S. Lander, E.L. Aiden, Cohesin loss eliminates all loop domains, Cell 171 (2) (2017) 305-320 e24.
[79] A. Vaharautio, J. Taipale, Cancer, Cancer by super-enhancer, Science 346 (6215) (2014) 1291–1292.
[80] D. Hnisz, A.S. Weintraub, D.S. Day, A.L. Valton, R.O. Bak, C.H. Li, J. Goldmann, B.R. Lajoie, Z.P. Fan, A.A. Sigova, J. Reddy, D. Borges-Rivera, T.I. Lee, R. Jaenisch, M.H. Porteus, J. Dekker, R.A. Young, Activation of proto-oncogenes by disruption of chromosome neighborhoods, Science 351 (6280) (2016) 1454–1458.
[81] B. Akhtar-Zaidi, R. Cowper-Sal-lari, O. Corradin, A. Saiakhova, C.F. Bartels, D. Balasubramanian, L. Myeroff, J. Lutterbaugh, A. Jarrar, M.F. Kalady, J. Willis, J.H. Moore, P.J. Tesar, T. Laframboise, S. Markowitz, M. Lupien, P.C. Scacheri, Epigenomic enhancer profiling defines a signature of colon cancer, Science 336 (6082) (2012) 736–739.
[82] Y. Jiang, Y.Y. Jiang, J.J. Xie, A. Mayakonda, M. Hazawa, L. Chen, J.F. Xiao, C.Q. Li, M.L. Huang, L.W. Ding, Q.Y. Sun, L. Xu, D. Kanojia, M. Jeitany, J.W. Deng, L.D. Liao, H.J. Soukiasian, B.P. Berman, J.J. Hao, L.Y. Xu, E.M. Li, M.R. Wang, X.G. Bi, D.C. Lin, H.P. Koeffler, Co-activation of super-enhancer-driven CCAT1 by TP63 and SOX2 promotes squamous cancer progression, Nat. Commun. 9 (1) (2018) 3619.
[83] M.G. Chheda, D.H. Gutmann, Using epigenetic reprogramming to treat pediatric brain cancer, Cancer Cell 31 (5) (2017) 609–611.
[84] W. Meng, J. Wang, B. Wang, F. Liu, M. Li, Y. Zhao, C. Zhang, Q. Li, J. Chen, L. Zhang, Y. Tang, J. Ma, CDK7 inhibition is a novel therapeutic strategy against GBM both in vitro and in vivo, Cancer Manag. Res. 10 (2018) 5747–5758.
[85] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (5) (2011) 646–674.
[86] T.I. Lee, R.A. Young, Transcriptional regulation and its misregulation in disease, Cell 152 (6) (2013) 1237–1251.
[87] P.A. Oldenborg, CD47: a cell surface glycoprotein which regulates multiple functions of hematopoietic cells in health and disease, ISRN Hematol 2013 (2013) 614619.
[88] S.B. Willingham, J.P. Volkmer, A.J. Gentles, D. Sahoo, P. Dalerba, S.S. Mitra, J. Wang, H. Contreras-Trujillo, R. Martin, J.D. Cohen, P. Lovelace, F.A. Scheeren, M.P. Chao, K. Weiskopf, C. Tang, A.K. Volkmer, T.J. Naik, T.A. Storm, A.R. Mosley, B. Edris, S.M. Schmid, C.K. Sun, M.S. Chua, O. Murillo, P. Rajendran, A.C. Cha, R.K. Chin, D. Kim, M. Adorno, T. Raveh, D. Tseng, S. Jaiswal, P.O. Enger, G.K. Steinberg, G. Li, S.K. So, R. Majeti, G.R. Harsh, M. van de Rijn, N.N. Teng, J.B. Sunwoo, A.A. Alizadeh, M.F. Clarke, I.L. Weissman, The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors, Proc. Natl. Acad. Sci. U. S. A. 109 (17) (2012) 6662–6667.
[89] P.A. Betancur, B.J. Abraham, Y.Y. Yiu, S.B. Willingham, F. Khameneh,

M. Zarnegar, A.H. Kuo, K. McKenna, Y. Kojima, N.J. Leeper, P. Ho, P. Gip, T. Swigut, R.I. Sherwood, M.F. Clarke, G. Somlo, R.A. Young, I.L. Weissman, A CD47-associated super-enhancer links pro-inflammatory signalling to CD47 up-regulation in breast cancer, Nat. Commun. 8 (2017) 14802.
[90] Xuejian Liu, Xia Wu, Yanming Wang, Yuhua Li, Xiangli Chen, Wenchuan Yang, Lihua Jiang, CD47 promotes human glioblastoma invasion through activation of the PI3K/Akt pathway, Oncol. Res. 27 (4) (2019) 415–422.
[91] F. Li, B. Lv, Y. Liu, T. Hua, J. Han, C. Sun, L. Xu, Z. Zhang, Z. Feng, Y. Cai, Y. Zou, Y. Ke, X. Jiang, Blocking the CD47-SIRPalpha axis by delivery of anti-CD47 antibody induces antitumor effects in glioma and glioma stem cells, Oncoimmunology 7 (2) (2018) e1391973.
[92] S. Gholamin, S.S. Mitra, A.H. Feroze, J. Liu, S.A. Kahn, M. Zhang, R. Esparza, C. Richard, V. Ramaswamy, M. Remke, A.K. Volkmer, S. Willingham, A. Ponnuswami, A. McCarty, P. Lovelace, T.A. Storm, S. Schubert, G. Hutter, C. Narayanan, P. Chu, E.H. Raabe, G.T. Harsh, M.D. Taylor, M. Monje, Y.J. Cho, R. Majeti, J.P. Volkmer, P.G. Fisher, G. Grant, G.K. Steinberg, H. Vogel, M. Edwards, I.L. Weissman, S.H. Cheshier, Disrupting the CD47-SIRPalpha anti-phagocytic axis by a humanized anti-CD47 antibody is an efficacious treatment for malignant pediatric brain tumors, Sci. Transl. Med. 9 (381) (2017).
[93] M. Conacci-Sorrell, L. McFerrin, R.N. Eisenman, An overview of MYC and its interactome, Cold Spring Harb. Perspect. Med. 4 (1) (2014) a014357.
[94] A.M. Gouw, K. Margulis, N.S. Liu, S.J. Raman, A. Mancuso, G.G. Toal, L. Tong, A. Mosley, A.L. Hsieh, D.K. Sullivan, Z.E. Stine, B.J. Altman, A. Schulze, C.V. Dang, R.N. Zare, D.W. Felsher, The MYC oncogene cooperates with sterol-regulated element-binding protein to regulate lipogenesis essential for neoplastic growth, Cell Metab. 30 (3) (2019) 556-572 e5.
[95] K. Misund, N. Keane, C.K. Stein, Y.W. Asmann, G. Day, S. Welsh, S.A. Van Wier, D.L. Riggs, G. Ahmann, M. Chesi, D.S. Viswanatha, S.K. Kumar, A. Dispenzieri, V. Gonzalez-Calle, R.A. Kyle, M. O'Dwyer, S.V. Rajkumar, K.M. Kortum, J.J. Keats, M.C. Network, R. Fonseca, A.K. Stewart, W.M. Kuehl, E. Braggio, P.L. Bergsagel, MYC dysregulation in the progression of multiple myeloma, Leukemia 34 (1) (2020) 322–326.
[96] D. Chen, Z. Zhao, Z. Huang, D.C. Chen, X.X. Zhu, Y.Z. Wang, Y.W. Yan, S. Tang, S. Madhavan, W. Ni, Z.P. Huang, W. Li, W. Ji, H. Shen, S. Lin, Y.Z. Jiang, Super enhancer inhibitors suppress MYC driven transcriptional amplification and tumor progression in osteosarcoma, Bone Res. 6 (2018) 11.
[97] T.R. Kress, A. Sabo, B. Amati, MYC: connecting selective transcriptional control to global RNA production, Nat. Rev. Cancer 15 (10) (2015) 593–607.
[98] X. Chen, F. Yang, T. Zhang, W. Wang, W. Xi, Y. Li, D. Zhang, Y. Huo, J. Zhang, A. Yang, T. Wang, MiR-9 promotes tumorigenesis and angiogenesis and is activated by MYC and OCT4 in human glioma, J. Exp. Clin. Cancer Res. 38 (1) (2019) 99.
[99] D. Annibali, J.R. Whitfield, E. Favuzzi, T. Jauset, E. Serrano, I. Cuartas, S. Redondo-Campos, G. Folch, A. Gonzalez-Junca, N.M. Sodir, D. Masso-Valles, M.E. Beaulieu, L.B. Swigart, M.M. Mc Gee, M.P. Somma, S. Nasi, J. Seoane, G.I. Evan, L. Soucek, Myc inhibition is effective against glioma and reveals a role for Myc in proficient mitosis, Nat. Commun. 5 (2014) 4632.
[100] G.L. Bidwell 3rd, E. Perkins, J. Hughes, M. Khan, J.R. James, D. Raucher, Thermally targeted delivery of a c-Myc inhibitory polypeptide inhibits tumor progression and extends survival in a rat glioma model, PLoS One 8 (1) (2013) e55104.
[101] F. Higuchi, A.L. Fink, J. Kiyokawa, J.J. Miller, M.V.A. Koerner, D.P. Cahill, H. Wakimoto, PLK1 inhibition targets myc-activated malignant glioma cells irrespective of mismatch repair deficiency-mediated acquired resistance to temozolomide, Mol. Cancer Ther. 17 (12) (2018) 2551–2563.
[102] F. Agustoni, K. Suda, H. Yu, S. Ren, C.J. Rivard, K. Ellison, C. Caldwell Jr., L. Rozeboom, K. Brovsky, F.R. Hirsch, EGFR-directed monoclonal antibodies in combination with chemotherapy for treatment of non-small-cell lung cancer: an updated review of clinical trials and new perspectives in biomarkers analysis, Cancer Treat. Rev. 72 (2019) 15–27.
[103] Q. Cao, X. You, L. Xu, L. Wang, Y. Chen, PAQR3 suppresses the growth of non-small cell lung cancer cells via modulation of EGFR-mediated autophagy, Autophagy (2019) 1–12.
[104] L. Pedrosa, F. Esposito, T.M. Thomson, J. Maurel, The tumor microenvironment in colorectal cancer therapy, Cancers (Basel) 11 (8) (2019).
[105] X. Chen, J.X. Loo, X. Shi, W. Xiong, Y. Guo, H. Ke, M. Yang, Y. Jiang, S. Xia, M. Zhao, S. Zhong, C. He, L. Fu, F. Li, E6 protein expressed by high-risk HPV activates super-enhancers of the EGFR and c-MET oncogenes by destabilizing the histone demethylase KDM5C, Cancer Res. 78 (6) (2018) 1418–1430.
[106] K.M. Kiang, X.Q. Zhang, G.P. Zhang, N. Li, S.Y. Cheng, M.W. Poon, J.K. Pu, W.M. Lui, G.K. Leung, CRNDE expression positively correlates with EGFR activation and modulates glioma cell growth, Target. Oncol. 12 (3) (2017) 353–363.
[107] D.G. Chen, B. Zhu, S.Q. Lv, H. Zhu, J. Tang, C. Huang, Q. Li, P. Zhou, D.L. Wang, G.H. Li, Inhibition of EGR1 inhibits glioma proliferation by targeting CCND1 promoter, J. Exp. Clin. Cancer Res. 36 (1) (2017) 186.
[108] N. Sakakini, L. Turchi, A. Bergon, H. Holota, S. Rekima, F. Lopez, P. Paquis, F. Almairac, D. Fontaine, N. Baeza-Kallee, E. Van Obberghen-Schilling, M.P. Junier, H. Chneiweiss, D. Figarella-Branger, F. Burel-Vandenbos, J. Imbert, T. Virolle, A positive feed-forward loop associating EGR1 and PDGFA promotes proliferation and self-renewal in glioblastoma stem cells, J. Biol. Chem. 291 (20) (2016) 10684–10699.
[109] P. Szturz, M. Budikova, J.B. Vermorken, I. Horova, B. Gal, E. Raymond, A. de Gramont, S. Faivre, Prognostic value of c-MET in head and neck cancer: a systematic review and meta-analysis of aggregate data, Oral Oncol. 74 (2017) 68–76.
[110] M. Boichuck, J. Zorea, M. Elkabets, M. Wolfson, V.E. Fraifeld, c-Met as a new marker of cellular senescence, Aging (Albany NY) 11 (9) (2019) 2889–2897.
[111] D. Pierscianek, Y.H. Kim, K. Motomura, M. Mittelbronn, W. Paulus, B. Brokinkel, K. Keyvani, K. Wrede, Y. Nakazato, Y. Tanaka, L. Mariani, A. Vital, U. Sure, H. Ohgaki, MET gain in diffuse astrocytomas is associated with poorer outcome, Brain Pathol. 23 (1) (2013) 13–18.
[112] Y. Kwak, S.I. Kim, C.K. Park, S.H. Paek, S.T. Lee, S.H. Park, C-MET overexpression and amplification in gliomas, Int. J. Clin. Exp. Pathol. 8 (11) (2015) 14932–14938.
[113] D.S. Kong, S.Y. Song, D.H. Kim, K.M. Joo, J.S. Yoo, J.S. Koh, S.M. Dong, Y.L. Suh, J.I. Lee, K. Park, J.H. Kim, D.H. Nam, Prognostic significance of c-Met expression in glioblastomas, Cancer 115 (1) (2009) 140–148.
[114] T. Fujiwara, GATA transcription factors: basic principles and related human disorders, Tohoku J. Exp. Med. 242 (2) (2017) 83–91.
[115] C. Vicente, A. Conchillo, M.A. Garcia-Sanchez, M.D. Odero, The role of the GATA2 transcription factor in normal and malignant hematopoiesis, Crit. Rev. Oncol. Hematol. 82 (1) (2012) 1–17.
[116] M. Achour, S. Le Gras, C. Keime, F. Parmentier, F.X. Lejeune, A.L. Boutillier, C. Neri, I. Davidson, K. Merienne, Neuronal identity genes regulated by super-enhancers are preferentially down-regulated in the striatum of Huntington's disease mice, Hum. Mol. Genet. 24 (12) (2015) 3481–3496.
[117] Z. Wang, H. Yuan, C. Sun, L. Xu, Y. Chen, Q. Zhu, H. Zhao, Q. Huang, J. Dong, Q. Lan, GATA2 promotes glioma progression through EGFR/ERK/Elk-1 pathway, Med. Oncol. 32 (4) (2015) 87.
[118] S. Coma, M. Allard-Ratick, T. Akino, L.A. van Meeteren, A. Mammoto, M. Klagsbrun, GATA2 and Lmo2 control angiogenesis and lymphangiogenesis via direct transcriptional regulation of neuropilin-2, Angiogenesis 16 (4) (2013) 939–952.
[119] L. Cedo, S.T. Reddy, E. Mato, F. Blanco-Vaca, J.C. Escola-Gil, HDL and LDL: potential new players in breast cancer development, J. Clin. Med. 8 (6) (2019).
[120] J. Yuan, Y.Y. Jiang, A. Mayakonda, M. Huang, L.W. Ding, H. Lin, F. Yu, Y. Lu, T.K.S. Loh, M. Chow, S. Savage, J.W. Tyner, D.C. Lin, H.P. Koeffler, Super-enhancers promote transcriptional dysregulation in nasopharyngeal carcinoma, Cancer Res. 77 (23) (2017) 6614–6626.
[121] R.A. Firestone, Low-density lipoprotein as a vehicle for targeting antitumor compounds to cancer cells, Bioconjug. Chem. 5 (2) (1994) 105–113.
[122] A.J. Versluis, P.C. Rensen, E.T. Rump, T.J. Van Berkel, M.K. Bijsterbosch, Low-density lipoprotein receptor-mediated delivery of a lipophilic daunorubicin derivative to B16 tumours in mice using apolipoprotein E-enriched liposomes, Br. J. Cancer 78 (12) (1998) 1607–1614.
[123] L. Maletinska, E.A. Blakely, K.A. Bjornstad, D.F. Deen, L.J. Knoff, T.M. Forte, Human glioblastoma cell lines: levels of low-density lipoprotein receptor and low-density lipoprotein receptor-related protein, Cancer Res. 60 (8) (2000) 2300–2303.
[124] T. Nekrasova, A. Minden, Role for p21-activated kinase PAK4 in development of the mammalian heart, Transgenic Res. 21 (4) (2012) 797–811.
[125] B.H. Ha, E.M. Morse, B.E. Turk, T.J. Boggon, Signaling, regulation, and specificity of the type II p21-activated kinases, J. Biol. Chem. 290 (21) (2015) 12975–12983.
[126] Y.Y. Jiang, D.C. Lin, A. Mayakonda, M. Hazawa, L.W. Ding, W.W. Chien, L. Xu, Y. Chen, J.F. Xiao, W. Senapedis, E. Baloglu, D. Kanojia, L. Shang, X. Xu, H. Yang, J.W. Tyner, M.R. Wang, H.P. Koeffler, Targeting super-enhancer-associated oncogenes in oesophageal squamous cell carcinoma, Gut 66 (8) (2017) 1358–1368.
[127] C.K. Rane, A. Minden, P21 activated kinase signaling in cancer, Semin. Cancer Biol. 54 (2019) 40–49.
[128] S.Y. Won, J.J. Park, E.Y. Shin, E.G. Kim, PAK4 signaling in health and disease: defining the PAK4-CREB axis, Exp. Mol. Med. 51 (2) (2019) 11.
[129] Y. Liu, H. Xiao, Y. Tian, T. Nekrasova, X. Hao, H.J. Lee, N. Suh, C.S. Yang, A. Minden, The pak4 protein kinase plays a key role in cell survival and tumorigenesis in athymic mice, Mol. Cancer Res. 6 (7) (2008) 1215–1224.
[130] D. Kesanakurti, C. Chetty, D. Rajasekhar Maddirela, M. Gujrati, J.S. Rao, Functional cooperativity by direct interaction between PAK4 and MMP-2 in the regulation of anoikis resistance, migration and invasion in glioma, Cell Death Dis. 3 (2012) e445.
[131] D. Kesanakurti, D. Maddirela, Y.K. Banasavadi-Siddegowda, T.H. Lai, Z. Qamri, N.K. Jacob, D. Sampath, S. Mohanam, B. Kaur, V.K. Puduvalli, A novel interaction of PAK4 with PPARgamma to regulate Nox1 and radiation-induced epithelial-to-mesenchymal transition in glioma, Oncogene 36 (37) (2017) 5309–5320.
[132] D.P. Bartel, MicroRNAs: genomics, biogenesis, mechanism, and function, Cell 116 (2) (2004) 281–297.
[133] R. Bhome, F. Del Vecchio, G.H. Lee, M.D. Bullock, J.N. Primrose, A.E. Sayan, A.H. Mirnezami, Exosomal microRNAs (exomiRs): small molecules with a big role in cancer, Cancer Lett. 420 (2018) 228–235.
[134] J. Lu, G. Getz, E.A. Miska, E. Alvarez-Saavedra, J. Lamb, D. Peck, A. Sweet-Cordero, B.L. Ebert, R.H. Mak, A.A. Ferrando, J.R. Downing, T. Jacks, H.R. Horvitz, T.R. Golub, MicroRNA expression profiles classify human cancers, Nature 435 (7043) (2005) 834–838.
[135] A. Esquela-Kerscher, F.J. Slack, Oncomirs - microRNAs with a role in cancer, Nat. Rev. Cancer 6 (4) (2006) 259–269.
[136] C.M. Croce, Causes and consequences of microRNA dysregulation in cancer, Nat. Rev. Genet. 10 (10) (2009) 704–714.
[137] W. Zhang, L. Wang, X. Pang, J. Zhang, Y. Guan, Role of microRNA-155 in modifying neuroinflammation and gamma-aminobutyric acid transporters in specific central regions after post-ischaemic seizures, J. Cell. Mol. Med. 23 (8) (2019) 5017–5024.
[138] H. Ji, D. Tian, B. Zhang, Y. Zhang, D. Yan, S. Wu, Overexpression of miR-155 in clear-cell renal cell carcinoma and its oncogenic effect through targeting FOXO3a, Exp. Ther. Med. 13 (5) (2017) 2286–2292.
[139] X.F. Zhang, R. Tu, K. Li, P. Ye, X. Cui, Tumor suppressor PTPRJ is a target of miR-155 in colorectal cancer, J. Cell. Biochem. 118 (10) (2017) 3391–3400.

[140] A. Martinez-Usatorre, L.F. Sempere, S.J. Carmona, L. Carretero-Iglesia, G. Monnot, D.E. Speiser, N. Rufer, A. Donda, D. Zehn, C. Jandus, P. Romero, MicroRNA-155 expression is enhanced by T-cell receptor stimulation strength and correlates with improved tumor control in Melanoma, Cancer Immunol. Res. 7 (6) (2019) 1013–1024.
[141] Q. Duan, X. Mao, Y. Xiao, Z. Liu, Y. Wang, H. Zhou, Z. Zhou, J. Cai, K. Xia, Q. Zhu, J. Qi, H. Huang, J. Plutzky, T. Yang, Super enhancers at the miR-146a and miR-155 genes contribute to self-regulation of inflammation, Biochim. Biophys. Acta 1859 (4) (2016) 564–571.
[142] J. Sun, H. Shi, N. Lai, K. Liao, S. Zhang, X. Lu, Overexpression of microRNA-155 predicts poor prognosis in glioma patients, Med. Oncol. 31 (4) (2014) 911.
[143] L. Yang, C. Li, F. Liang, Y. Fan, S. Zhang, MiRNA-155 promotes proliferation by targeting caudal-type homeobox 1 (CDX1) in glioma cells, Biomed. Pharmacother. 95 (2017) 1759–1764.
[144] M.V. Puccetti, C.M. Adams, T.D. Dan, A. Palagani, B.A. Simone, T. DeAngelis, C.M. Eischen, N.L. Simone, MicroRNA-21 is required for hematopoietic cell viability after radiation exposure, Int. J. Radiat. Oncol. Biol. Phys. 104 (5) (2019) 1165–1174.
[145] H.I. Suzuki, R.A. Young, P.A. Sharp, Super-enhancer-mediated rna processing revealed by integrative MicroRNA network analysis, Cell 168 (6) (2017) 1000-1014 e15.
[146] C.H. Yang, J. Yue, S.R. Pfeffer, M. Fan, E. Paulus, A. Hosni-Ahmed, M. Sims, S. Qayyum, A.M. Davidoff, C.R. Handorf, L.M. Pfeffer, MicroRNA-21 promotes glioblastoma tumorigenesis by down-regulating insulin-like growth factor-binding protein-3 (IGFBP3), J. Biol. Chem. 289 (36) (2014) 25079–25087.
[147] M.S. Masoudi, E. Mehrabian, H. Mirzaei, MiR-21: a key player in glioblastoma pathogenesis, J. Cell. Biochem. 119 (2) (2018) 1285–1290.
[148] C. Chai, L.J. Song, S.Y. Han, X.Q. Li, M. Li, MicroRNA-21 promotes glioma cell proliferation and inhibits senescence and apoptosis by targeting SPRY1 via the PTEN/PI3K/AKT signaling pathway, CNS Neurosci. Ther. 24 (5) (2018) 369–380.
[149] D. Dong, N. Fu, P. Yang, MiR-17 downregulation by high glucose stabilizes thioredoxin-interacting protein and removes thioredoxin inhibition on ASK1 leading to apoptosis, Toxicol. Sci. 150 (1) (2016) 84–96.
[150] H. Weng, H. Huang, B. Dong, P. Zhao, H. Zhou, L. Qu, Inhibition of miR-17 and miR-20a by oridonin triggers apoptosis and reverses chemoresistance by derepressing BIM-S, Cancer Res. 74 (16) (2014) 4409–4419.
[151] E. Hasvik, T. Schjolberg, D.P. Jacobsen, A.J. Haugen, L. Grovle, E.I. Schistad, J. Gjerstad, Up-regulation of circulating microRNA-17 is associated with lumbar radicular pain following disc herniation, Arthritis Res. Ther. 21 (1) (2019) 186.
[152] B. Malzkorn, M. Wolter, F. Liesenberg, M. Grzendowski, K. Stuhler, H.E. Meyer, G. Reifenberger, Identification and functional characterization of microRNAs involved in the malignant progression of gliomas, Brain Pathol. 20 (3) (2010) 539–550.
[153] S. Lu, S. Wang, S. Geng, S. Ma, Z. Liang, B. Jiao, Increased expression of microRNA-17 predicts poor prognosis in human glioma, J. Biomed. Biotechnol. 2012 (2012) 970761.
[154] L. Xiao, J. Wu, J.Y. Wang, H.K. Chung, S. Kalakonda, J.N. Rao, M. Gorospe, J.Y. Wang, Long noncoding RNA uc.173 promotes renewal of the intestinal mucosa by inducing degradation of MicroRNA 195, Gastroenterology 154 (3) (2018) 599–611.
[155] L. Zhang, X. Meng, X.W. Zhu, D.C. Yang, R. Chen, Y. Jiang, T. Xu, Long non-coding RNAs in Oral squamous cell carcinoma: biologic function, mechanisms and clinical implications, Mol. Cancer 18 (1) (2019) 102.
[156] K. Zhou, C. Zhang, H. Yao, X. Zhang, Y. Zhou, Y. Che, Y. Huang, Knockdown of long non-coding RNA NEAT1 inhibits glioma cell migration and invasion via modulation of SOX2 targeted by miR-132, Mol. Cancer 17 (1) (2018) 105.
[157] J. Ji, R. Xu, K. Ding, G. Bao, X. Zhang, B. Huang, X. Wang, A. Martinez, X. Wang, G. Li, H. Miletic, F. Thorsen, R. Bjerkvig, L. Xiang, B. Han, A. Chen, X.G. Li, J. Wang, Long noncoding RNA SChLAP1 forms a growth promoting complex with HNRNPL in human glioblastoma through stabilization of ACTN4 and activation of NF-kappaB signaling, Clin. Cancer Res. 25 (22) (2019) 6868–6881.
[158] Y. Jiang, W. Cao, K. Wu, X. Qin, X. Wang, Y. Li, B. Yu, Z. Zhang, X. Wang, M. Yan, Q. Xu, J. Zhang, W. Chen, LncRNA LINC00460 promotes EMT in head and neck squamous cell carcinoma by facilitating peroxiredoxin-1 into the nucleus, J. Exp. Clin. Cancer Res. 38 (1) (2019) 365.
[159] J. Xu, Q. Meng, X. Li, H. Yang, J. Xu, N. Gao, H. Sun, S. Wu, G. Familiari, M. Relucenti, H. Zhu, J. Wu, R. Chen, Long non-coding RNA MIR17HG promotes colorectal cancer progression via miR-17-5p, Cancer Res. 79 (19) (2019) 4882–4895.
[160] K.M. Kiang, X.Q. Zhang, G.K. Leung, Long non-coding RNAs: the key players in Glioma Pathogenesis, Cancers (Basel) 7 (3) (2015) 1406–1424.
[161] N. Malissovas, E. Ninou, A. Michail, P.K. Politis, Targeting long non-coding RNAs in nervous system cancers: new insights in prognosis, diagnosis and therapy, Curr Med Chem 26 (30) (2018) 5649–5663.
[162] B. Alaiyan, N. Ilyayev, A. Stojadinovic, M. Izadjoo, M. Roistacher, V. Pavlov, V. Tzivin, D. Halle, H. Pan, B. Trink, A.O. Gure, A. Nissan, Differential expression of colon cancer associated transcript1 (CCAT1) along the colonic adenoma-carcinoma sequence, BMC Cancer 13 (2013) 196.
[163] J.F. Xiang, Q.F. Yin, T. Chen, Y. Zhang, X.O. Zhang, Z. Wu, S. Zhang, H.B. Wang, J. Ge, X. Lu, L. Yang, L.L. Chen, Human colorectal cancer-specific CCAT1-L lncRNA regulates long-range chromatin interactions at the MYC locus, Cell Res. 24 (5) (2014) 513–531.
[164] Z.H. Wang, X.Q. Guo, Q.S. Zhang, J.L. Zhang, Y.L. Duan, G.F. Li, D.L. Zheng, Long non-coding RNA CCAT1 promotes glioma cell proliferation via inhibiting microRNA-410, Biochem. Biophys. Res. Commun. 480 (4) (2016) 715–720.
[165] B. Cui, B. Li, Q. Liu, Y. Cui, lncRNA CCAT1 promotes Glioma Tumorigenesis by sponging miR-181b, J. Cell. Biochem. 118 (12) (2017) 4548–4557.
[166] S.B. Cogill, L. Wang, Co-expression network analysis of human lncRNAs and cancer genes, Cancer Informat. 13 (Suppl. 5) (2014) 49–59.
[167] J. Zhao, Y. Liu, W. Zhang, Z. Zhou, J. Wu, P. Cui, Y. Zhang, G. Huang, Long non-coding RNA Linc00152 is involved in cell cycle arrest, apoptosis, epithelial to mesenchymal transition, cell migration and invasion in gastric cancer, Cell Cycle 14 (19) (2015) 3112–3123.
[168] Q. Cai, Z.Q. Wang, S.H. Wang, C. Li, Z.G. Zhu, Z.W. Quan, W.J. Zhang, Upregulation of long non-coding RNA LINC00152 by SP1 contributes to gallbladder cancer cell growth and tumor metastasis via PI3K/AKT pathway, Am. J. Transl. Res. 8 (10) (2016) 4068–4081.
[169] Q.N. Chen, X. Chen, Z.Y. Chen, F.Q. Nie, C.C. Wei, H.W. Ma, L. Wan, S. Yan, S.N. Ren, Z.X. Wang, Long intergenic non-coding RNA 00152 promotes lung adenocarcinoma proliferation via interacting with EZH2 and repressing IL24 expression, Mol. Cancer 16 (1) (2017) 17.
[170] E. Huang, R. Liu, Y. Chu, miRNA-15a/16: as tumor suppressors and more, Future Oncol. 11 (16) (2015) 2351–2363.
[171] M. Yu, Y. Xue, J. Zheng, X. Liu, H. Yu, L. Liu, Z. Li, Y. Liu, Linc00152 promotes malignant progression of glioma stem cells by regulating miR-103a-3p/FEZF1/CDC25A pathway, Mol. Cancer 16 (1) (2017) 110.
[172] S. Souquere, G. Beauclair, F. Harper, A. Fox, G. Pierron, Highly ordered spatial organization of the structural long noncoding NEAT1 RNAs within paraspeckle nuclear bodies, Mol. Biol. Cell 21 (22) (2010) 4020–4027.
[173] D. Chakravarty, A. Sboner, S.S. Nair, E. Giannopoulou, R. Li, S. Hennig, J.M. Mosquera, J. Pauwels, K. Park, M. Kossai, T.Y. MacDonald, J. Fontugne, N. Erho, I.A. Vergara, M. Ghadessi, E. Davicioni, R.B. Jenkins, N. Palanisamy, Z. Chen, S. Nakagawa, T. Hirose, N.H. Bander, H. Beltran, A.H. Fox, O. Elemento, M.A. Rubin, The oestrogen receptor alpha-regulated lncRNA NEAT1 is a critical modulator of prostate cancer, Nat. Commun. 5 (2014) 5383.
[174] M.Z. Ma, B.F. Chu, Y. Zhang, M.Z. Weng, Y.Y. Qin, W. Gong, Z.W. Quan, Long non-coding RNA CCAT1 promotes gallbladder cancer development via negative modulation of miRNA-218-5p, Cell Death Dis. 6 (2015) e1583.
[175] C. He, B. Jiang, J. Ma, Q. Li, Aberrant NEAT1 expression is associated with clinical outcome in high grade glioma patients, APMIS 124 (3) (2016) 169–174.
[176] Q. Chen, J. Cai, Q. Wang, Y. Wang, M. Liu, J. Yang, J. Zhou, C. Kang, M. Li, C. Jiang, Long noncoding RNA NEAT1, regulated by the EGFR pathway, contributes to glioblastoma progression through the WNT/beta-catenin pathway by scaffolding EZH2, Clin. Cancer Res. 24 (3) (2018) 684–695.
[177] X. Cao, L. Dang, X. Zheng, Y. Lu, Y. Lu, R. Ji, T. Zhang, X. Ruan, J. Zhi, X. Hou, X. Yi, M.J. Li, T. Gu, M. Gao, L. Zhang, Y. Chen, Targeting super-enhancer-driven oncogenic transcription by CDK7 inhibition in anaplastic thyroid carcinoma, Thyroid 29 (6) (2019) 809–823.
[178] C.H. Chen, N. Yang, Y. Zhang, J. Ding, W. Zhang, R. Liu, W. Liu, C. Chen, Inhibition of super enhancer downregulates the expression of KLF5 in basal-like breast cancers, Int. J. Biol. Sci. 15 (8) (2019) 1733–1742.
[179] M.R. McKeown, M.R. Corces, M.L. Eaton, C. Fiore, E. Lee, J.T. Lopez, M.W. Chen, D. Smith, S.M. Chan, J.L. Koenig, K. Austgen, M.G. Guenther, D.A. Orlando, J. Loven, C.C. Fritz, R. Majeti, Superenhancer analysis defines novel epigenomic subtypes of non-APL AML, including an RARalpha dependency targetable by SY-1425, a potent and selective RARalpha agonist, Cancer Discov. 7 (10) (2017) 1136–1153.
[180] S.C. Mack, K.W. Pajtler, L. Chavez, K. Okonechnikov, K.C. Bertrand, X. Wang, S. Erkek, A. Federation, A. Song, C. Lee, X. Wang, L. McDonald, J.J. Morrow, A. Saiakhova, P. Sin-Chan, Q. Wu, K.A. Michaelraj, T.E. Miller, C.G. Hubert, M. Ryzhova, L. Garzia, L. Donovan, S. Dombrowski, D.C. Factor, B. Luu, C.L.L. Valentim, R.C. Gimple, A. Morton, L. Kim, B.C. Prager, J.J.Y. Lee, X. Wu, J. Zuccaro, Y. Thompson, B.L. Holgado, J. Reimand, S.Q. Ke, A. Tropper, S. Lai, S. Vijayarajah, S. Doan, V. Mahadev, A.F. Minan, S.N. Grobner, M. Lienhard, M. Zapatka, Z. Huang, K.D. Aldape, A.M. Carcaboso, P.J. Houghton, S.T. Keir, T. Milde, H. Witt, Y. Li, C.J. Li, X.W. Bian, D.T.W. Jones, I. Scott, S.K. Singh, A. Huang, P.B. Dirks, E. Bouffet, J.E. Bradner, V. Ramaswamy, N. Jabado, J.T. Rutka, P.A. Northcott, M. Lupien, P. Lichter, A. Korshunov, P.C. Scacheri, S.M. Pfister, M. Kool, M.D. Taylor, J.N. Rich, Therapeutic targeting of ependymoma as informed by oncogenic enhancer profiling, Nature 553 (7686) (2018) 101–105.
[181] G. Manzotti, A. Ciarrocchi, V. Sancisi, Inhibition of BET proteins and histone deacetylase (HDACs): crossing roads in cancer therapy, Cancers (Basel) 11 (3) (2019).
[182] J.E. Jang, J.I. Eom, H.K. Jeung, J.W. Cheong, J.Y. Lee, J.S. Kim, Y.H. Min, AMPK-ULK1-mediated autophagy confers resistance to BET inhibitor JQ1 in acute myeloid leukemia stem cells, Clin. Cancer Res. 23 (11) (2017) 2781–2794.
[183] J.M. Cooper, A.J. Patel, Z. Chen, C.P. Liao, K. Chen, J. Mo, Y. Wang, L.Q. Le, Overcoming BET inhibitor resistance in malignant peripheral nerve sheath tumors, Clin. Cancer Res. 25 (11) (2019) 3404–3416.
[184] J. Zuber, J. Shi, E. Wang, A.R. Rappaport, H. Herrmann, E.A. Sison, D. Magoon, J. Qi, K. Blatt, M. Wunderlich, M.J. Taylor, C. Johns, A. Chicas, J.C. Mulloy, S.C. Kogan, P. Brown, P. Valent, J.E. Bradner, S.W. Lowe, C.R. Vakoc, RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia, Nature 478 (7370) (2011) 524–528.
[185] Y. Han, S. Lindner, Y. Bei, H.D. Garcia, N. Timme, K. Althoff, A. Odersky, A. Schramm, A. Lissat, A. Kunkele, H.E. Deubzer, A. Eggert, J.H. Schulte, A.G. Henssen, Synergistic activity of BET inhibitor MK-8628 and PLK inhibitor Volasertib in preclinical models of medulloblastoma, Cancer Lett. 445 (2019) 24–33.
[186] P. Zhang, R. Li, H. Xiao, W. Liu, X. Zeng, G. Xie, W. Yang, L. Shi, Y. Yin, K. Tao, BRD4 inhibitor AZD5153 suppresses the proliferation of colorectal cancer cells

and sensitizes the anticancer effect of PARP inhibitor, Int. J. Biol. Sci. 15 (9) (2019) 1942–1954.
[187] A.S. Bhagwat, J.S. Roe, B.Y.L. Mok, A.F. Hohmann, J. Shi, C.R. Vakoc, BET bromodomain inhibition releases the mediator complex from select cis-regulatory elements, Cell Rep. 15 (3) (2016) 519–530.
[188] S. Nagaraja, N.A. Vitanza, P.J. Woo, K.R. Taylor, F. Liu, L. Zhang, M. Li, W. Meng, A. Ponnuswami, W. Sun, J. Ma, E. Hulleman, T. Swigut, J. Wysocka, Y. Tang, M. Monje, Transcriptional dependencies in diffuse intrinsic pontine glioma, Cancer Cell 31 (5) (2017) 635-652 e6.
[189] F. Liu, W. Jiang, Y. Sui, W. Meng, L. Hou, T. Li, M. Li, L. Zhang, J. Mo, J. Wang, Y. Zhao, L. Zhang, J. Ma, Y. Tang, CDK7 inhibition suppresses aberrant hedgehog pathway and overcomes resistance to smoothened antagonists, Proc. Natl. Acad. Sci. U. S. A. 116 (26) (2019) 12986–12995.
[190] Y. Xia, L.Y. Lin, M.L. Liu, Z. Wang, H.H. Hong, X.G. Guo, G.Q. Gao, Selective inhibition of CDK7 ameliorates experimental arthritis in mice, Clin. Exp. Med. 15 (3) (2015) 269–275.
[191] J.R. Huang, W.M. Qin, K. Wang, D.R. Fu, W.J. Zhang, Q.W. Jiang, Y. Yang, M.L. Yuan, Z.H. Xing, M.N. Wei, Y. Li, Z. Shi, Cyclin-dependent kinase 7 inhibitor THZ2 inhibits the growth of human gastric cancer in vitro and in vivo, Am. J. Transl. Res. 10 (11) (2018) 3664–3676.
[192] S. Sampathi, P. Acharya, Y. Zhao, J. Wang, K.R. Stengel, Q. Liu, M.R. Savona, S.W. Hiebert, The CDK7 inhibitor THZ1 alters RNA polymerase dynamics at the 5' and 3' ends of genes, Nucleic Acids Res. 47 (8) (2019) 3921–3936.
[193] N. Kwiatkowski, T. Zhang, P.B. Rahl, B.J. Abraham, J. Reddy, S.B. Ficarro, A. Dastur, A. Amzallag, S. Ramaswamy, B. Tesar, C.E. Jenkins, N.M. Hannett, D. McMillin, T. Sanda, T. Sim, N.D. Kim, T. Look, C.S. Mitsiades, A.P. Weng, J.R. Brown, C.H. Benes, J.A. Marto, R.A. Young, N.S. Gray, Targeting transcription regulation in cancer with a covalent CDK7 inhibitor, Nature 511 (7511) (2014) 616–620.
[194] J.M. Dowen, Z.P. Fan, D. Hnisz, G. Ren, B.J. Abraham, L.N. Zhang, A.S. Weintraub, J. Schujiers, T.I. Lee, K. Zhao, R.A. Young, Control of cell identity genes occurs in insulated neighborhoods in mammalian chromosomes, Cell 159 (2) (2014) 374–387.
[195] L. Tögel, R. Nightingale, A.C. Chueh, A. Jayachandran, H. Tran, T. Phesse, R. Wu, O.M. Sieber, D. Arango, A.S. Dhillon, M.A. Dawson, B. Diez-Dacal, T.C. Gahman, P. Filippakopoulos, A.K. Shiau, J.M. Mariadason, Dual targeting of bromodomain and extraterminal domain proteins, and WNT or MAPK signaling, inhibits c-MYC expression and proliferation of colorectal cancer cells, Mol. Cancer Ther. 15 (6) (2016) 1217–1226.
[196] Yan Yi Jiang, De Chen Lin, Anand Mayakonda, Masaharu Hazawa, Ling Wen Ding, Wen Wen Chien, Liang Xu, Ye Chen, Jin Fen Xiao, William Senapedis, Erkan Baloglu, Deepika Kanojia, Li Shang, Xin Xu, Henry Yang, Jeffrey Tyner, Ming Rong Wang, H. Phillip Koeffler, Targeting super-enhancer-associated oncogenes in oesophageal squamous cell carcinoma, Gut 66 (8) (2017) 1358–1368.
[197] J. Yuan, Y.Y. Jiang, A. Mayakonda, M. Huang, L.W. Ding, H. Lin, F. Yu, Y. Lu, Loh TKS, M. Chow, S. Savage, J.W. Tyner, D.C. Lin, H.P. Koeffler, Super-enhancers promote transcriptional dysregulation in nasopharyngeal carcinoma, Cancer Res. 77((23) (2017) 6614–6626.