REVIEW

Epigenetic plasticity of enhancers in cancer

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ABSTRACT

Enhancers are cis-acting elements with many sites bound by transcription factors and activate transcription over long distance. Histone modifications are critical for enhancer activity and utilized as hallmarks for the identification of putative enhancers. Monomethylation of histone H3 lysine 4 (H3K4me1) is the mark for enhancer priming; acetylation of histone H3 lysine 27 (H3K27ac) for active enhancers and trimethylation of histone H3 lysine 27 (H3K27me3) for silent enhancers. Recent studies from multiple groups have provided evidence that enhancer reprogramming, especially gain of enhancer activity, is closely related to tumorigenesis and cancer development. In this review, we will summarize the recent discoveries about enhancer regulation and the mechanisms of enhancer reprogramming in tumorigenesis, and discuss the potential application of enhancer manipulation in precision medicine.

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Introduction

The human genome contains about 20,000 protein-coding genes according to different databases [1–3], which is less than that in *Arabidopsis thaliana* [4]. The reason of higher biological complexity in human is due to the precise and complicated transcription regulation [5]. Precise temporal and spatial gene expressions are regulated by cis-acting regulatory elements such as promoters, enhancers, and insulators. Among these, enhancers play central roles in controlling selective gene transcription during cell differentiation and development [6]. An enhancer is one fragment of noncoding DNA sequence with multiple transcription factor binding sites, which regulates gene transcription at a long distance [7].

The patterns of enhancer distributions are now often used for the identification of cell types and differentiation states [8–10]. It is estimated that millions of putative enhancers exist in the human genome [11]. Enhancers not only act on their neighbor genes but also regulate genes faraway [12]. Moreover, the enhancers for one gene may vary in different cells. For example, in pancreatic cancer, the enhancer driving *MYC* expression is located near the transcription termination site of

Myc gene; and in T-cell acute lymphoblastic leukemia, the enhancer is located downstream of the gene; while in colorectal cancer, the enhancer is located upstream of the gene [13]. In the human genome, the number of enhancers is far more than that of genes [14]. In some cases, one enhancer regulates multiple genes according to the context [15]. For example, enhancers located between *Dppa5a* and *Ooep* have been shown to regulate the transcription of both genes simultaneously in mouse embryonic stem (ES) cells [16]. It has long been accepted that one gene is regulated by multiple enhancers. Five enhancers near *Dppa5a* have been predicted [16]; and in mouse brain tissue four enhancers near the *Aristaless*-related homeobox (*Arx*) gene regulate its transcription, which is closely related to neurodevelopment [17]. To study the complex network between enhancers and genes, various techniques have been developed to predict and identify enhancers and their target genes in the genome.

In 2013, Richard A. Young's laboratory proposed the concept of super-enhancers based on their ChIP-Seq studies of transcription factors and related histone modifications [18]. Super-enhancers (SEs) are large clusters of transcriptional enhancers enriched with high-density of key transcription factors, cofactors,

and enhancer-specific epigenetic modifications. SEs drive the expression of key genes for cell identity, and have great potential in studies of developmental biology and disease pathogenesis [19–21]. Some SEs are distributed in genomic regions close to disease-specific genes, so they are of great value in disease diagnosis and treatment [22]. A recent study identified nearly 1700 SEs from 42 ependymoma patients, which were specific activated in tumor cells. The authors further identified 15 SEs critical for most ependymoma cancer cells. Without any of the 15 SEs, the cancer cell viability declined at least 50% [23]. The work from our lab studied the change of histone modifications in MMTV-PyVT breast cancer mice, and identified 661 super-enhancers with high activity in breast cancer tissues by H3K27ac ChIP-Seq analysis [24]. Oncogenes are often overexpressed in cancer cells and activated by hyper-active super-enhancers during tumorigenesis. A recent study identified the specific super-enhancer of glioma stem cells (GSCs) and 148 super-enhancer target genes. With the analysis of TCGA and other databases, the authors identified that a GSCs-specific super-enhancer upregulated *ELOVL2*, a key polyunsaturated fatty acid synthesis enzyme. Further experiments showed that *ELOVL2* catalyzes the production of long-chain polyunsaturated fatty acids, maintains cell membrane composition and stabilizes EGFR signaling pathway, thus promoting the survival and proliferation of GSCs [25].

Increasing studies have shown that enhancer regulation and reprogramming are closely related to tumorigenesis and cancer development [26–28]. Therefore, it is critical to explore the molecular mechanism of enhancer dynamics to understand the processes of tumorigenesis and cancer development. In this review, we will introduce the relationship between histone modifications and enhancer activity and the recent technical advances for enhancer annotation. Then, we will also discuss the current understanding about enhancer reprogramming in cancer.

Features and annotation of enhancers

The history of enhancer studies is almost 40 years. In 1981, Banerji et al. found a 140 bp sequence upstream of an SV40 early gene containing two 72 bp tandem repeats. A plasmid inserted with the

sequence increased the expression of rabbit β -globin gene in HeLa cells more than 200 times, thus the DNA fragment was named as an enhancer for one kind of cis-regulatory elements [29]. Enhancers play a central role in precisely regulating spatiotemporal transcription which is critical for the growth and development of eukaryotes organisms [30,31]. Identification and annotation of distant regulatory enhancers is the key to understand mechanisms regulating cell-type-specific transcription. It was time-consuming and laborious to determine the position and activity of enhancers with classical experimental methods [32]. With the development of Next Generation Sequencing (NGS) technology, many novel techniques have been developed to identify and annotate millions of putative enhancers, such as DNase-seq, FAIRE-seq, ChIP-Seq, and ATAC-seq [32–35].

The most important feature for enhancers is that they are specific DNA sequences bound by transcription factors (TFs) [36]. Binding of TFs usually is required for enhancer activation. For example, pioneer factor FoxA2 binds to enhancers to stimulate transcription in liver [37]. Pioneer factors alone are not sufficient to activate transcription, and they usually function through facilitating the accessibility of chromatin. Consequently, they recruit transcription co-factors and other regulatory proteins to chromatin [38], such as histone-modifying enzymes p300/CBP and MLL3/4, as well as chromatin remodelers and mediator complex for crosstalk between enhancers and promoters [39]. A study has shown that HOXA9 overexpression in leukemia leads to significant enhancer reprogramming and activation of new leukemia-specific enhancers. As a pioneer factor, HOXA9 firstly binds to new enhancer sites and then facilitates the recruitment of CEBP α and MLL3/MLL4 complexes to establish epigenetic landscape [40]. Then, transcription initiation complexes, including RNA Polymerase II (RNAPII), are recruited to enhancers to induce gene transcription [41].

ChIP-seq profiles of these co-factors are now widely used to predict enhancers [42]. Visel et al. identified thousands of enhancer sites in forebrain, midbrain, and limb tissues of mouse embryos by using p300 ChIP-seq [43]. In addition to co-factors, histone variant H3.3 has also been reported to mark active enhancers. H3.3 and typical histone H3 differ only in five amino acids. H3.3 does not affect the

stability of single nucleosome; however, H3.3 can destroy the spatial structure of chromatin, and make enhancer regions accessible for transcription factor binding [44]. Recently, Martire, S. et al. found that the phosphorylation of serine 31 of histone H3.3 enhances the acetyltransferase activity of p300 in a trans-acting manner and increases H3K27ac level on enhancers in mESCs. Compared with wild type mESCs, the absence of H3.3 reduces H3K27ac of enhancers during differentiation, which in turn affects cell fate [45].

Another important feature for enhancers is the specific epigenetic signature of histone modifications enriched on them [46]. Several histone modifications have been found to be critical for enhancer activity. Usually, H3K4me1 is the basic mark to label enhancers. If H3K27ac is also present, the enhancer is active; if H3K27me3 occupies the region instead of H3K27ac, the enhancer is poised [6]. Nowadays, scientists are using ChIP-Seq of histone modifications to annotate enhancers. For example, Creighton et al. defined the chromatin regions enriched with H3K4me1 but not H3K4me3 as enhancers, and predicted 25,036 enhancers in mESCs. Subsequently, they found that the proximal genes of the enhancers lacking H3K27ac showed lower expression level than the average level of the proximal genes of all enhancers, indicating H3K27ac as a hallmark for active enhancers [47]. H3K27ac enriched regions in intergenic chromatin are now often used to identify active enhancers [22,23,48]. Generally, H3K4me3 marks the gene transcription start sites (TSS) and enhancers are far away from them [32,46]. However, it was reported recently that H3K4me3 also exists in some overactive enhancers, which was proposed to be associated with tumorigenesis [24,49]. Core et al. found that the ratio of H3K4me3/H3K4me1 on the active enhancer was positively correlated with transcription levels of enhancers which suggesting that H3K4 methylation patterns may correlate with transcription levels [50]. Interestingly, some regions near TSS are found to be modified by H3K4me1 and H3K27ac. These regions not only possess the epigenetic characteristics of enhancers but also regulate the transcription of distant genes. Researchers named these genome elements near TSS with enhancer activity as Epromoters [51].

Another strategy to annotate enhancer is using enhancer-templated non-coding RNAs (eRNAs),

RNAs transcribed from enhancers [52,53]. Most eRNAs are short, unstable, non-polyadenylate and low-expressed non-coding RNAs [54]. eRNA E2-3 is transcribed from the distal enhancer of human heme oxygenase-1 gene (*HO-1*); when it was knocked down with siRNA, the transcription of *HO-1* was significantly inhibited [55]. In another study, MUNC was identified as an eRNA upstream of *MYOD* gene, promoting its expression [56]. These results indicate that eRNAs play important roles in transcription regulation. Two mechanisms are suggested for eRNAs in regulating transcription. One is that eRNAs may interact with cohesin and mediator complex to stabilize the looping structure of the enhancer and promoter; and the other is that eRNAs may promote promoter region chromatin accessibility [54]. Bose et al. found that the interaction between acetyltransferase CBP and eRNAs promotes its acetyltransferase activity, which elevates H3K27ac and H3K18ac on the enhancer and promoter regions, thus promoting transcription [57]. eRNAs are often used as the hallmark for active enhancer [58–61], however sometimes it is challenging to measure eRNA level since the amounts of certain eRNAs are too low to be detected by RT-PCR [62,63].

ChIP-Seq technology is now widely used for enhancer annotation but often not sufficient for determining the target gene of a specific enhancer, since the distance between enhancers and target genes is highly variable, and enhancers can be at the upstream or downstream of its target gene or sometimes in introns and even on different chromosome [64,65]. Chromosome conformation capture (3C) technique and its derivative technology (4C, 5C, Hi-C, ChIA-PET, and Hi-ChIP) have been developed to study the three-dimensional structure of chromatin with super-resolution and high throughput sequencing [66]. 3C technology studies the point-to-point chromatin interactions, that is, the interactions between two chromatin loci, such as enhancers and promoters. Stadhouders et al. used 3C technology to prove that enhancers within the *Myb-Hbs1l* intergenic region interacted with *Myb* promoter, thus promoting *Myb* expression in proliferating cells [67]. However, 3C can only detect chromatin interaction between two loci. In 2006, Chromosome Conformation Capture on a Chip (4C) was developed to study the interaction between one genomic locus and multiple loci [66]. Using 4C

technology combined with NGS sequencing, Mermet et al. studied the genome-wide regions interacting with Cryptochrome 1 (*Cry1*) promoter, and identified enhancers affecting *Cry1* transcription [68]. In order to study the interaction of many-to-many chromatin interactions, 3C-Carbon Copy (5C) technology was developed. 5C allows a more comprehensive analysis of chromatin cyclized interactions of genes by drawing interaction maps between multiple loci in parallel [69]. Subsequent Hi-C and Chromatin Interaction Analysis by Paired-End Tag (ChIA-PET) were developed to study more complex and sophisticated spatial organization of genomes [66]. HiChIP, a method that combines in situ Hi-C and transposase-mediated on-bead library construction, can capture chromatin interactions mediated by specific proteins. Compared with ChIA-PET, HiChIP is more efficient and sensitive [70]. These techniques, usually integrated with ChIP-Seq and RNA-Seq, are used to illustrate chromatin 3D structure and enhancer-promoter interactions.

Dynamic epigenetic modifications on enhancers

As discussed above, the active enhancers are occupied by H3K4me1 and H3K27ac, while the poised enhancers by H3K4me1 and H3K27me3. Histone modifications are closely related to enhancer status and now used to determine enhancer activity [6]. Epigenetic factors including “writers and erasers” have been reported to play important roles in various biological processes through modulating enhancer activity (Figure 1).

MLL3/MLL4 are members of COMPASS family and have H3K4 methyltransferase activity. MLL3/MLL4 complexes contain weak trimethylation activity and are responsible for H3K4me1/2 in cells [71]. Several studies showed that MLL3 and MLL4 bind to enhancers, catalyze H3K4me1, and recruit histone acetyltransferase (HAT) p300 to activate enhancers by catalyzing H3K27ac [72–74]. Therefore, it is believed that MLL3/MLL4 promotes enhancer activity dependent on its methyltransferase activity [75]. However, Dorigi et al. showed that in mESCs the catalytic-deficient Mll3/4 mutant still contained the ability to regulate enhancers and gene transcription. While double knock-out of Mll3/4 resulted in

Figure 1. Histone modification enzymes regulating enhancers. A brief summary of epigenetic enzymes including “writers and erasers” regulating enhancer activity. MLL3/4 and CBP/p300 are responsible for building up the hallmarks of enhancers, H3K4me1 and H3K27ac, respectively. While, some of the enzymes may regulate enhancers through recruiting other enzymes or cofactors, independent of their catalytic activity.

a significant decrease of H3K27ac, eRNA and target gene transcription. Therefore, the authors believed that the activation of Mll3/4 on enhancer had nothing to do with their catalytic activity [76]. Later, Yan et al. provided evidence that MLL3/4 methyltransferase activity was required for enhancer and promoter interactions at the Sox2 locus [77]. The function of H3K4me1 in enhancer regulation still requires more studies, while MLL3/MLL4 is certainly critical for many biological processes through regulating enhancer activity [78,79].

Besides MLL3/MLL4, many epigenetic modification enzymes have been reported to regulate enhancer activity. Histone acetyltransferase TIP60 recruits H3K4 methyltransferase MLL1 to enhancers of estrogen receptor (ER) α target genes and promotes estrogen-induced transcription through catalyzing H3K4me1 and H2AK5ac on enhancers [80]. SET7/9, a methyltransferase of H3K4me1, interacts with MyoD on the enhancers of skeletal muscle differentiation genes and activates transcription during differentiation [81]. Lysine-specific demethylase 1 (LSD1) is a histone demethylase for H3K4me1/2 and H3K9me1/2. It is recruited to the *MyoD* enhancer and helps RNA polymerase II recruitment through H3K9 demethylation, thus promoting eRNA and gene transcription during muscle differentiation [82]. The H3K4me2/3 demethylase KDM5C is recruited to enhancers through interacting with a chromatin reader RACK7 and prevents over-activation of enhancers and their target genes in breast

Table 1. Summary of epigenetic modification enzymes regulating enhancers.

Gene	Catalytic sites	Effect on enhancer activity	Mechanism	Biological function
MLL3/MLL4	H3K4me1/2 methyltransferase	Promotion	Catalytic activity [77] or recruiting p300 [76]	Repression in multiple cancers [85]
CBP/p300	H3K27 acetyltransferase	Promotion	Catalytic activity [86]	Repression or promotion in different cancers [87]
TIP60	H2AK5, H3K14, H4K5/8/12/16 acetyltransferase	Promotion	Catalytic activity [80]	Repression or promotion in different cancers [88]
SET7/9	H3K4me1 methyltransferase	Promotion	Catalytic activity and recruiting MyoD	Promoting myoblast differentiation ^[81]
LSD1/KDM1A	H3K4me1/2 and H3K9me1/2 demethylase	Promotion or repression	Catalytic activity	Promoting myogenesis [82]; Promoting prostate cancer [89] and leukemia [90]
KDM3A	H3K9me1/2 demethylase	Promotion	Catalytic activity and recruiting p300	Promoting colorectal cancer [83] and prostate cancer [91]
KDM5C	H3K4me2/3 demethylase	Repression	Catalytic activity	Repressing cervical carcinoma [92] and breast cancer [49]
UTX/KDM6A	H3K27me2/3 demethylase	Promotion	Catalytic activity or Recruiting MLL4	Promoting innate inflammatory ^[93] Repressing cardiomyocyte apoptosis ^[94] Repressing myeloid leukemogenesis ^[95]

cells [49]. Our recent study showed that histone demethylase KDM3A removes H3K9me1/2 on enhancers, recruits p300 and activates the target genes of hippo signaling pathway in colorectal cancer [83]. Histone modifying enzymes may also regulate enhancer activity in an enzyme activity-independent manner. The H3K27 demethylase UTX/KDM6A promotes enhancer activity in embryonic stem cells by facilitating the recruitment of MLL4 and p300, and the subsequent H3K4me1 and H3K27ac, in a demethylase-independent manner [84]. For more information on epigenetic modification enzymes regulating enhancers, see Table 1.

Mutation of enhancer-associated genes in cancer

The function and potential usage of epigenetics in cancer have been discussed in many reports, however few studies have shown that epigenetic abnormality leads to tumorigenesis without genetic defects [96]. In the majority of cancer patients, genetic and epigenetic alterations happen together in cancer cells. GWAS studies revealed that epigenetics genes are one of the largest groups of frequently mutated genes in cancer [97]. Interestingly, almost all the key histone modification enzymes known to regulate enhancers show high mutation rates in genetic sequencing analysis. Based on TCGA data, the key enzymes in MLL3/4 complex and p300/CBP histone acetyltransferase are frequently mutated in multiple types of cancer (Figure 2). Lu et al. found that the mutation in the PHD domain of MLL3 results in the defect of BAP1 recruitment to the enhancers of tumor-suppressor genes, which represses enhancer activity and promotes tumorigenesis [98]. In breast cancer, KDM5C mutation causes trimethylation of H3K4 and overactivation of oncogene enhancers, which in turn promotes oncogene expression and tumorigenesis [42]. Nevertheless, the mechanisms of how these mutations promote cancer still need to be fully addressed.

Current information points to a potential connection between cancer and enhancer dysregulation. Pioneer studies have been done with animal models and showed that targeting an enhancer regulatory network might be a promising strategy for cancer treatment. JQ1 is a small molecular inhibitor for BRD4, the critical factor recognizing

Figure 2. Mutations in enhancer-associated factors. The percentage of patients affected by the indicated gene mutations in all types of cancers is shown. PTEN (phosphatase and tensin homolog) is a well-known tumor suppressor and used as comparison here. Data are from TCGA database. KMT2D, lysine methyltransferase 2D, also named as MLL4; KDM2C, lysine methyltransferase 2D, also named as MLL3; CREBBP, CREB binding protein, also named as CBP; EP300, E1A binding protein p300, also named as p300; KDM6A, lysine demethylase 6A, also named as UTX; KDM5C, lysine demethylase 5C, also named as JARID1C; KDM3A, lysine demethylase 3A, also named as JMJD1A; KDM1A, lysine demethylase 1A, also named as LSD1; KAT5, lysine acetyltransferase 5, also named as TIP60; SETD7, SET domain containing 7, also named as SET7/9.

histone acetylation on enhancers. It has been shown to effectively repress cancer cells [99]. In addition to JQ1, many BET bromodomain inhibitors such as CPI-0610 and TEN-010 are in clinical development for the treatment of various tumors. These inhibitors can reduce the activity of oncogene enhancers by inhibiting BET binding to acetylated histones [100]. As summarized above, histone demethylase LSD1 can promote cancers by regulating the activity of enhancers. GSK2879552 and INCB059872, inhibitors of LSD1, are also in the clinical experimental stage, and mainly used for the treatment of acute myeloid leukemia (AML) and small cell lung cancer [101]. C646, a potent inhibitor for P300/CBP, has been shown to repress breast cancer in an animal model [24]. So, enhancer dysregulation is one of the critical aspects of cancer, though the underlying mechanisms still require extensive work.

Mutation occurring in the enhancers of cancer-related genes

Genetic and epigenetic changes promote the occurrence and development of tumors synergistically

[102]. Genome-wide association studies (GWAS) have identified numerous genome loci associated with cancer. However, most of the cancer-associated single nucleotide polymorphism (SNP) loci are located on the non-coding regions and their functional connections with cancer are not determined yet. Enhancer may function through these intergenic SNPs to regulate tumorigenesis and metastasis. Song et al. analyzed cancer risk-associated SNPs and found that breast cancer risk-related SNP rs11055880 was located on a distal enhancer. Further experiments showed that the enhancer regulated the nearest gene *ATF7IP*, 100 kb downstream of the SNP. Two SNPs, rs11055880-C and rs11055880-T, could significantly improve *ATF7IP* transcription. Therefore, the relationship between rs11055880 locus and breast cancer susceptibility may be related to the regulation of *ATF7IP* expression level [103]. SNPs may function through destroying transcription factor binding sites on enhancers and inhibit enhancer activity. For example, SNP rs539846 localizes in a super-enhancer near *BMF* in chronic lymphocytic leukemia. rs539846-A inhibits enhancer activity and *BMF* expression by inhibiting *RELA* binding [104]. Collectively, SNP in non-coding cis-regulatory elements such as enhancers can promote oncogenesis through abnormal enhancer activity.

In addition to SNPs, other genetic variants including chromosomal translocations and copy number amplifications can alter enhancer activity in tumorigenesis [13]. Chromosomal translocations can change the target genes of the enhancer. For example, in adenoid cystic carcinoma (ACC), translocation occurring in the chromosome 6 (6q) can cause the reallocation of *NFIB* or *TGFBR3* super-enhancers to either upstream or downstream of the *MYB* gene, with consequent transcription activation [105]. Copy number amplifications in enhancer regions usually lead to over activation of target genes. For example, *MYC* is activated through focal amplification of distal enhancers in many cancers including acute lymphoblastic leukemia and neuroblastomas [13,106].

Enhancer reprogramming in tumorigenesis

Recent studies have found that epigenomic reprogramming, especially enhancer reprogramming, plays an important role in cancer progression and metastasis. It has been reported that the enhancers of

some proto-oncogenes are more active in human ependymoma tissues [23]. Epigenome-wide associate studies (EWAS) recently have been developed to identify cancer-associated enhancers. The initial study was performed using H3K4me1 ChIP-Seq [47]. Later, H3K27ac ChIP-Seq has been widely used to identify active enhancers in several cancers [26]. Through the above approaches, novel transcription factors were identified to play important roles in cancer development by promoting enhancer reprogramming. For example, FOXA1 was found to be highly expressed in pancreatic ductal adenocarcinoma and induce enhancer remodeling and promotes tumor migration [48]. Transcription factor TP63 is highly expressed in squamous subtypes of pancreatic ductal adenocarcinoma, and TP63-driven enhancer reprogramming promotes invasion of cancer cells [107]. However, the systematic studies of cancer-specific enhancers are still lacking for many types of cancers.

The cancer cells in one tumor often originate from different clones and cause heterogeneity of tumors, and the different enhancer profiles also exist among these heterogenous cells, which may provide a new method for identifying the subtypes or subsets of tumors. For example, neuroblastoma is usually classified into four subtypes by biochemical and genetic analysis. However, a new subtype was found when analyzing the enhancer profiles of the four subtypes [108]. Profiling the reprogrammed enhancers in tumor tissues is not only a new approach to predict tumors subtypes but also provides new candidates for cancer treatment.

Perspectives

The evidence has tightly connected cancer with enhancer regulation. In cancer cells, dysregulated enhancers mainly function through two ways to promote oncogenesis. One is that enhancers are overactivated by upstream signals or genetic mutation and cause oncogene overexpression; the other is that enhancers for tumor suppressors are repressed or genetic mutated which causes inactivation of tumor suppressors (Figure 3). Usually, H3K27ac signal on the locus is widely used to evaluate the enhancer activity.

Scientists have started experiments to treat cancer by manipulating enhancers. Tumor-related

Figure 3. Enhancer reprogramming in tumorigenesis. (a) Overview for the hyper-active enhancer activity of oncogenes in cancer cells. Pioneer factors, such as FOXA1, HOXA9, and TP63, bind to enhancers and facilitate the recruitment of co-factors, such as p300, to promote oncogenic enhancer activity. Moreover, some tumor suppressors, such as KDM5C, are mutated which promotes the hyper-activation of oncogenic enhancers. (b) Overview for the repression of tumor suppressive enhancers in cancer cells. The key enzymes for enhancer regulation including p300/CBP and MLL3/4 are frequently mutated in cancer cells. SNPs in enhancers can destroy transcription factor binding sites, directly inactivating enhancers and leading to transcriptional down-regulation of tumor-suppressor genes.

enhancers, especially those targeting oncogenes, provide good targets for precision medicine. Mack et al. screened drugs for ependymoma special enhancers, and eventually found a small molecule chemical that specifically inhibited the enhancer activity of oncogene *CACNA1H*. The chemical prolonged the survival time of ependymoma mice by 40%, and hardly affected the survival of normal tissue cells [23]. The experiment shows that enhancers are feasible for cancer treatment and tumor-related enhancers can provide targets for rare diseases. Enhancers are essential elements for transcriptional regulation and cell fate decision, and may be utilized as important biomarkers and drug targets for many diseases.

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