Pharmacology & Therapeutics 199 (2019) 129–138

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Super-enhancers in cancer

Palaniraja Thandapani [a,b,*]

[a] Department of Pathology, New York University School of Medicine, New York, NY 10016, USA
[b] Laura & Isaac Perlmutter Cancer Center, New York University School of Medicine, New York, NY 10016, USA

ARTICLE INFO

Keywords:
Super-enhancers
Cancer
Genetic variants
3D chromatin architecture
Enhancer hijacking
Transcriptional inhibitors

ABSTRACT

Cancer is fueled by the aberrant activity of oncogenic and tumor suppressive pathways. Transcriptional dysregulation of these pathways play a major role both in the genesis and development of cancer. Dysregulation of transcriptional programs can be mediated by genetic and epigenetic alterations targeting both protein coding genes and non-coding regulatory elements like enhancers and super-enhancers. Super-enhancers, characterized as large clusters of enhancers in close proximity, have been identified as essential oncogenic drivers required for the maintenance of cancer cell identity. As a result, cancer cells are often addicted to the super-enhancer driven transcriptional programs. Furthermore, pharmacological inhibitors targeting key components of super-enhancer assembly and activation have shown great promise in reducing tumor growth and proliferation in several preclinical tumor models. This article reviews the current understanding of super-enhancer assembly and activation, the different mechanisms by which cancer cells acquire oncogenic super-enhancers and, finally, the potential of targeting super-enhancers as future therapeutics.

© 2019 Elsevier Inc. All rights reserved.

Contents

1. Introduction

Our view of the regulatory genome has changed drastically in recent years. It is now clear that transcriptional activation defining cellular state is controlled by a combination of cell type specific proximal and distal regulatory elements, known as enhancers. Enhancers are functionally defined as noncoding elements that can activate transcription of a linearly distant gene, independent of its genomic orientation, through long-range *cis* chromatin interactions (Bulger & Groudine, 2011). In addition to typical enhancers, the genome is also comprised of large stretches of enhancers in close linear proximity, often spanning several kilobases in size, called super-enhancers (Whyte et al., 2013). Enhancers and super-enhancers alike, are occupied by the same components generally associated with enhancer activity, including transcription factors (TFs), co-activators such as the Mediator complex, chromatin regulators and the RNA polymerase II (pol II) complex. However, super-enhancers are unique in that they harbor these factors on an average 10-fold higher density than typical enhancers (Hnisz et al., 2013; Loven et al., 2013; Whyte et al., 2013). As a result, super-enhancers can drive higher levels of transcription of their target genes than typical enhancers (Fig. 1a). Super-enhancer influence on gene expression can be either additive of their individual enhancers,

Abbreviations: TF, Transcription factor; pol II, Polymerase II; H3K4me1, Histone H3 lysine 4 monomethylation; H3K27ac, Histone H3 lysine 27 acetylation; CTCF, CCCTC-binding factor; TAD, Topological associating domain; MED1, Mediator 1; YY1, Ying Yang 1; BRD, Bromodomain and extra terminal domain; CDK, Cyclin dependent kinase; IDH, Isocitrate dehydrogenase; TAL1, T cell acute lymphoblastic leukemia 1; T-ALL, T-cell acute lymphoblastic leukemia; AML, Acute myeloid leukemia; SNP, Single nucleotide polymorphism; CTD, Carboxy terminal domain..

* Corresponding author at: 550 First Avenue, Smilow 1303, New York, NY 10016, USA.
E-mail address: palaniraja.thandapani@nyumc.org.

https://doi.org/10.1016/j.pharmthera.2019.02.014
0163-7258/© 2019 Elsevier Inc. All rights reserved.

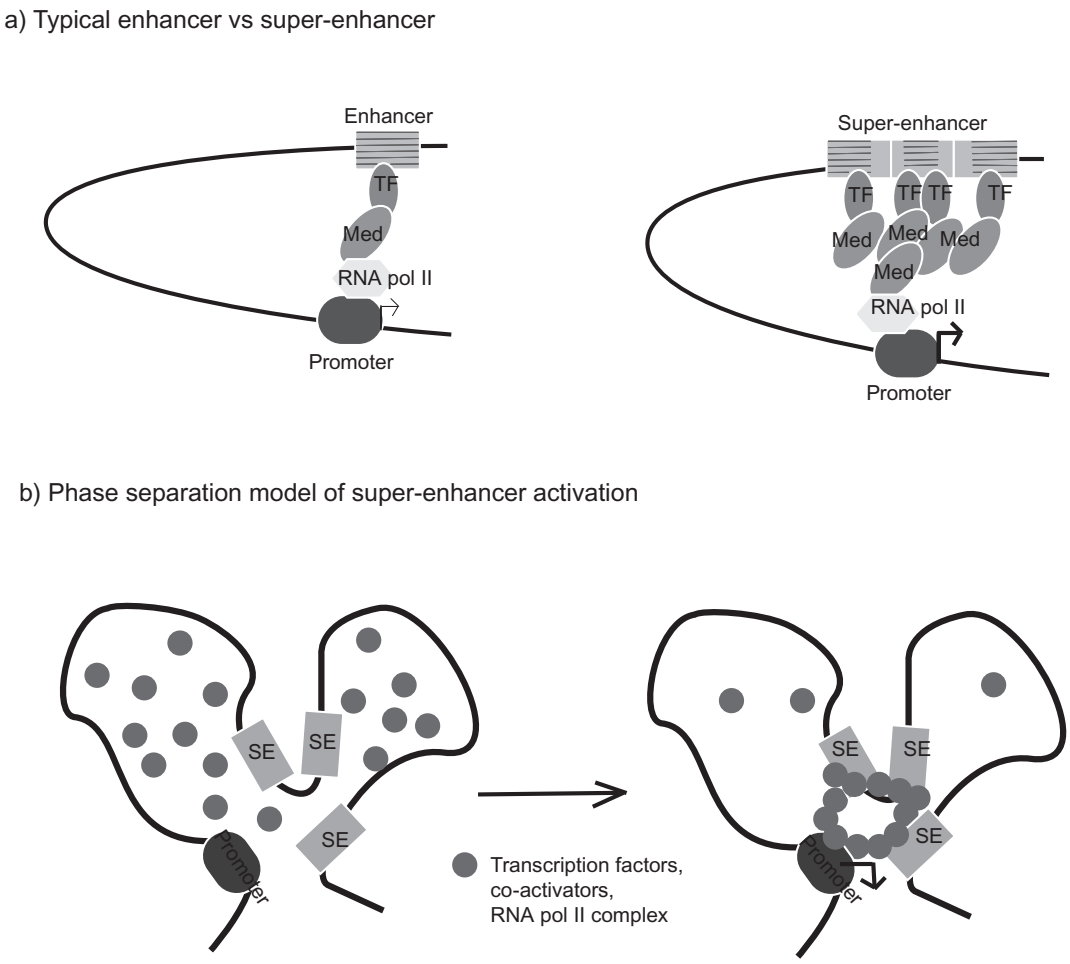

Fig. 1. Super-enhancer organization and activation. a) Schematic depiction of a typical enhancer and a super-enhancer. Enhancers and super-enhancers are bound by the same factors including transcription factors, co-activators, RNA pol II complex. However, super-enhancers are longer in length and are occupied by higher density of these transcriptional regulators. Enhancer elements within the stitched super-enhancer are highlighted by striped lines. b) A phase separation model of transcriptional activation by super-enhancers. High density interactions of transcriptional regulators can lead to the formation of phase separated multi molecular complex at the super-enhancer locus leading to frequent transcriptional bursts.

or can have a temporal and functional hierarchy within the constitutive enhancers (Hay et al., 2016; Hnisz et al., 2015; Shin et al., 2016).

Super-enhancers were initially identified in mouse embryonic stem cells (ESC) based on the high-density occupancy of ESC specific master transcription factors OCT4, SOX2 and NANOG at regulatory enhancers nearby genes that define ESC identity (Whyte et al., 2013). Subsequently, super-enhancers were identified in a broad array of cell types based on the enrichment of cell type specific master transcription factors nearby genes that dictate the biology of these cell types (Hnisz et al., 2013; Whyte et al., 2013). Following these initial observations, a role for super-enhancers in cancer development was suggested when several genetic variations within super-enhancers were identified in various cancer subtypes (D. Hnisz et al., 2013; Sengupta & George, 2017; Sur & Taipale, 2016). In addition, super-enhancers were found to regulate expression of key oncogenic drivers in many tumor samples (Bradner, Hnisz, & Young, 2017; Loven et al., 2013), suggesting that cancer cells are often addicted to the super-enhancer driven transcriptional programs (Bradner et al., 2017). This unique dependency of cancer cells combined with the extreme sensitivity of super-enhancers to perturbation of components associated with most enhancers has opened up new opportunities for targeting super-enhancers in cancer. In this review, we briefly summarize the current model of super-enhancer assembly and activation, discuss the different mechanisms by which cancer cells acquire or activate super-enhancers to upregulate oncogenic transcriptional programs, and finally explore the promising avenue of targeting super-enhancers using pharmacological inhibitors for future cancer therapeutics.

2. Super-enhancers: organization and activation

A central feature of enhancers and super-enhancers is that they contain clustered binding sites for multiple TFs. This enables the coordinated binding of multiple TFs, including master TFs and transcriptional effectors of signaling pathways, ensuring integration of intrinsic and extrinsic environmental cues at these elements (Yan et al., 2013). Occupancy of TFs at enhancers and super-enhancers are associated with regions of nucleosomal depletion and increased DNA accessibility as measured by hypersensitivity to DNA nucleases, such as the DNase I (Gross & Garrard, 1988). Nucleosomes flanking these TF binding sites have a distinct chromatin signatures including, but not limited to, histone H3 lysine 4 monomethylation (H3K4me1), histone H3 lysine 27 acetylation (H3K27ac) (Consortium et al., 2012; Roadmap Epigenomics et al., 2015). In fact, preferential enrichment of the H3K4me1 mark over H3K4me3 is often used to differentiate enhancers from active promoters (Heintzman et al., 2007), whereas H3K27ac distinguishes active enhancers from inactive/poised enhancers containing H3K4me1 (Creyghton et al., 2010). These two modifications in combination with nuclease hypersensitivity data or coactivator occupancy of Mediator 1 provide a robust readout of active enhancers, and have often been utilized for enhancer and super-enhancer annotation in numerous studies.

Binding of pioneering TF is the primary event that primes enhancer/super-enhancer elements for activation by the subsequent recruitment of co-activator proteins such as histone modifiers, ATP-dependent

chromatin remodelers and Mediator complex (Calo & Wysocka, 2013). The importance of the binding of pioneering TF in super-enhancer activation is highlighted by the fact that insertional mutations leading to generation of *de novo* TF binding site can trigger cooperative binding of multiple TFs and co-activators resulting in the activation of the super-enhancer element (Brown et al., 2014; Mansour et al., 2014). Activated super-enhancer facilitate long range physical interaction that bring the super-enhancer and promoter in close 3D proximity via looping out the intervening DNA sequence. The resultant chromatin loops enable interactions with the basal RNA pol II transcription machinery at target promoters to activate transcription (Levine, Cattoglio, & Tjian, 2014; Spitz & Furlong, 2012). The importance of this spatial interaction for transcriptional activation is highlighted by the fact that forced looping between β-globin promoter and enhancers 40 kb apart triggers transcription (Deng et al., 2012), providing a causal link between spatial interaction and transcriptional activation (Chen et al., 2018). However, the mechanism and the factors that mediate the physical interaction between enhancers and target promoter is not yet clearly understood. It was previously shown that cohesin binding is enriched at promoters and enhancers that forms chromatin loops (Kagey et al., 2010). Further immunoprecipitation assays confirmed interaction of cohesin with Mediator complex suggesting cohesin and mediator interaction could bridge enhancer-promoter contacts. It remains unclear if there are additional structural regulators that can mediate enhancer-promoter interactions. A recent report implicated TF, Yin Yang 1 (YY1), in mediating physical enhancer-promoter interactions both involving typical enhancers and super-enhancers (Weintraub et al., 2017). YY1 acts as a dimer and is a ubiquitously expressed protein that binds enhancers and promoters across cell types. Perturbation of YY1 binding disrupts enhancer-promoter interactions and associated gene expression.

In addition to the classical model of the orderly recruitment of TFs and transcriptional co-activators in super-enhancer assembly and activation, a phase separation model particularly for super-enhancer assembly and activation has recently been proposed (Hnisz, Shrinivas, Young, Chakraborty, & Sharp, 2017). High density conglomerates of proteins and nucleic acids and cooperative interactions amongst them can lead to phase separation and formation of membraneless organelles (Bergeron-Sandoval, Safaee, & Michnick, 2016). This is a now a well-recognized mechanism for the assembly of ribonucleoprotein granules like processing bodies (p-bodies) and stress granules (Brangwynne et al., 2009; Molliex et al., 2015). Since super-enhancers are hubs of high density interactions of transcriptional regulators and nucleic acids that exhibit rapid formation following a single nucleation event (Brown et al., 2014; Mansour et al., 2014), and dissolution following the deletion of the nucleation site (Hnisz et al., 2015; Shin et al., 2016) or upon pharmacological depletion of high-density factors from the super-enhancer region (Chapuy et al., 2013; Chipumuro et al., 2014; Kwiatkowski et al., 2014; Loven et al., 2013; Wang et al., 2015), a potential role for phase separation in super-enhancer activation is being explored (Fig. 1b). In support of this hypothesis, a recent report identified transcriptional co-activators like BRD4 and MED1 which are bound at high density at super-enhancers can form nuclear condensates at the sites of super-enhancer mediated transcription (Sabari et al., 2018). The authors further demonstrated that the phase separation properties of BRD4 and MED1 are mediated by their large intrinsically disordered regions (IDRs) that share properties with IDRs of several proteins that were previously reported to facilitate condensate formation (Banani, Lee, Hyman, & Rosen, 2017; Shin & Brangwynne, 2017). A similar role of initiating formation of phase separated condensates was also identified for the activation domains of master TFs OCT4 and GCN4 along with Mediator complex bound to super-enhancers (Boija et al., 2018). These reports have opened up a new model of transcriptional control by regulatory elements like super-enhancers that also explains different aspects of super-enhancer biology including formation, activation and extreme sensitivity to perturbations of its high-density coactivators (Hnisz et al., 2017).

3. Mechanisms of super-enhancer driven oncogenesis

Acquisition of super-enhancers driving expression of oncogenes can be broadly mediated by i) genetic variations that target the core super-enhancer element itself or ii) genetic variations that modify the 3D genome by disrupting higher order chromatin organization leading to oncogene activation by inadvertent super-enhancer promoter looping.

3.1. Genetic variations that affect the core super-enhancer element

Large scale genome-wide studies have uncovered that somatic variations commonly associated with disease frequently occur in the non-coding genome, and are often enriched within regulatory regions including enhancers and super-enhancers (Maurano et al., 2012; Schaub, Boyle, Kundaje, Batzoglou, & Snyder, 2012). Genetic alterations targeting super-enhancers, such as genomic deletions, duplications, inversions, insertions, translocations or single nucleotide polymorphisms (SNPs), can modify the copy number of super-enhancers, alter its genomic space, disrupt TF binding sites in putative super-enhancers that can either activate or repress super-enhancer function, all potential mechanisms resulting in the deregulation of nearby target genes (Krijger & de Laat, 2016; Spielmann, Lupianez, & Mundlos, 2018). In this section, several examples of how genetic variations targeting the core super-enhancer element can lead to oncogenic activation will be discussed.

Copy number variations such as super-enhancer amplification is a common mechanism of oncogenic activation (Fig. 2a). Somatic copy number analysis combined with tissue specific epigenetic profiling in 12 tumor types led to the identification of focal amplification of super-enhancers nearby putative oncogenes including *KLF5*, *USP12*, *PARD6B* and *MYC* (Zhang et al., 2016). In another study, systematic examination of chromosomal rearrangements in a large cohort of breast cancers identified 33 hotspots of tandem duplications (>100 kb) most of which were enriched in breast-tissue specific super-enhancer elements (Glodzik et al., 2017). These super-enhancer elements regulated the expression of individual oncogenes, including *MYC* and *ESR1*. In addition to copy number changes, genomic rearrangements such as inversions or translocations, as well as deletions, can place super-enhancers in new genomic context. Super-enhancers, as promiscuous regulatory elements, can now activate proto-oncogenes in their new genomic context. This phenomenon also known as 'enhancer hijacking' has been widely reported in cancer (Krijger & de Laat, 2016). One such translocation of a super-enhancer element was identified to mediate overexpression of the oncogenic TF, MYB, in adenoid cystic carcinoma (Drier et al., 2016). Epigenetic analysis confirmed the generation of a novel chimeric super-enhancer element nearby the *MYB* oncogene. Further chromatin conformation capture analysis confirmed chromatin interactions between the *MYB* promoter and the aberrantly translocated super-enhancer. Moreover, the translocated super-enhancer element was identified to harbor MYB binding sites that were actively bound by MYB itself leading to a positive feedback loop that further enhanced MYB expression in the samples harboring this translocation. Another example of enhancer hijacking was observed in the medulloblastoma subtypes group 3 and 4, particularly amongst the samples with high expression of growth factor independent 1 family proto-oncogenes, GFI1 and GFI1B (Northcott et al., 2014). Most of these cases had recurrent structural variations that resulted in the relocation of *GIF1* and *GIF1B* in close proximity to active super-enhancers, initiating oncogenic activity. In acute myeloid leukemia (AML), a 9 kb inversion event redirected a super-enhancer element from the *GATA2* tumor suppressor gene to the *EV1* oncogene that led to simultaneous oncogenic activation and downregulation of a tumor suppressor (Groschel et al., 2014; Yamazaki et al., 2014).

Oncogenic super-enhancers can also be established as a result of acquired somatic mutations within the super-enhancer element that leads to the creation of *de novo* binding sites for master TFs. Binding of a master TF can activate the super-enhancer element by recruiting additional

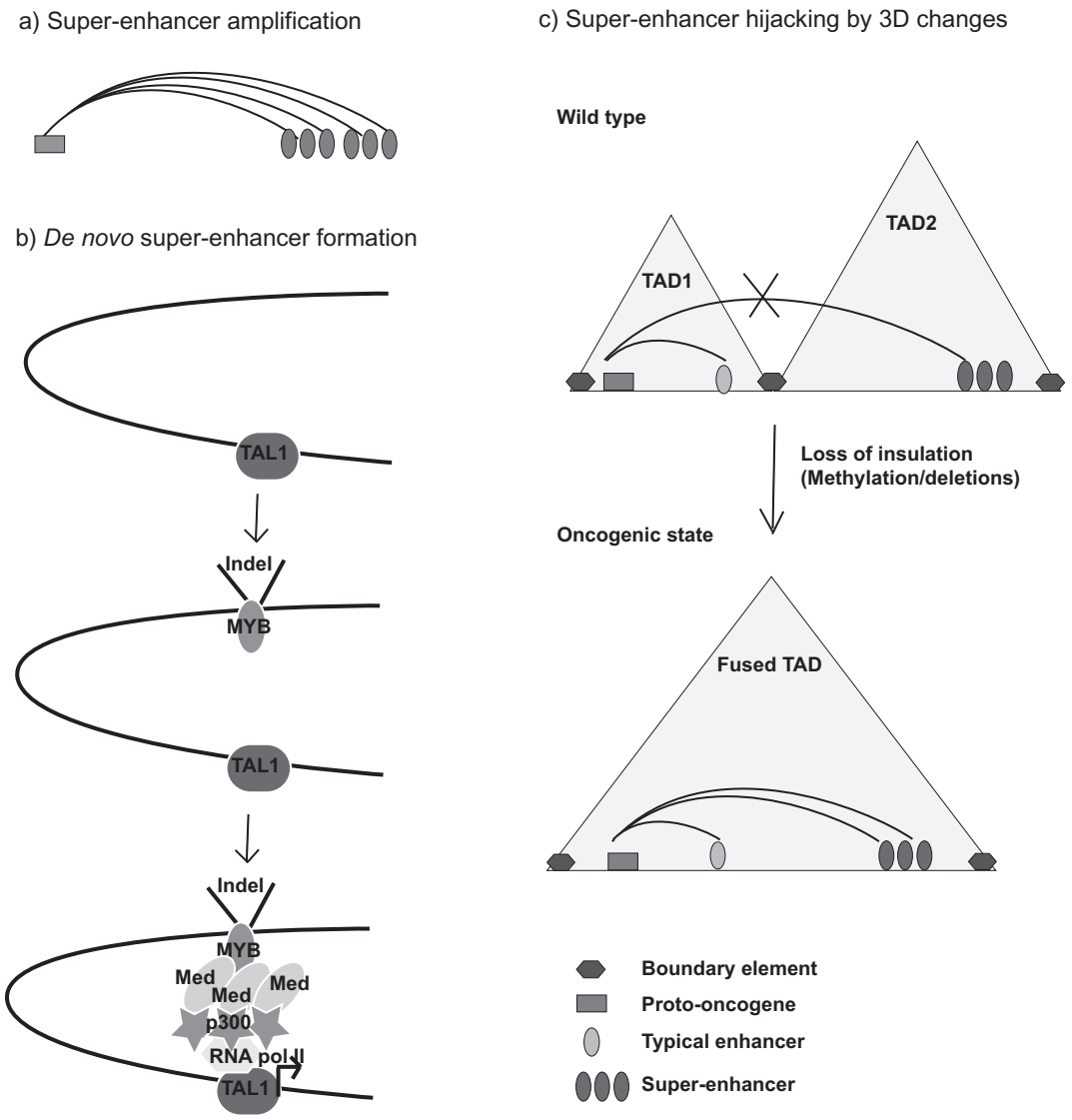

Fig. 2. Different mechanisms of Oncogenic super-enhancer formation. a) Focal amplification of super-enhancers can upregulate expression of driver oncogenes. b) Insertional mutations that introduce *de novo* transcription factor binding sites can enable nucleation and super-enhancer activation regulating expression a neighboring proto-oncogene. c) Structural variation or epigenetic deregulation can alter 3D chromatin architecture leading to aberrant super-enhancer promoter interactions resulting in increased expression of neighboring oncogenes.

co-activators resulting in transcriptional upregulation of a neighboring proto-oncogene. Mansour and colleagues observed that a subset of T-ALL samples expressed high levels of DNA binding TF, TAL1 (Mansour et al., 2014). However, this TAL1 overexpression was not associated with large chromosomal rearrangements near the *TAL1* gene, commonly identified in T-ALL samples with high TAL1 expression. While assessing the regulatory landscape near the *TAL1* gene through observation of the H3K27ac chromatin state commonly associated with active promoter and enhancer activity, the authors observed an active super-enhancer region proximal to the *TAL1* promoter not observed in T-ALL samples that lacked TAL1 overexpression. Targeted sequencing of this region led to the identification of small insertions of 2-18 bp that introduced *de novo* binding sites for the TF MYB. Further experiments confirmed MYB binding to these *de novo* binding sites that was essential for the downstream recruitment of several other TFs to this super-enhancer element to maintain an active enhancer state and drive the expression of the oncogene TAL1 (Fig. 2b). In addition to insertional mutations, single nucleotide polymorphisms (SNPs) can sometimes directly alter the super-enhancer activity in cancer. One such SNP was identified in the *LMO1* gene locus and was associated with neuroblastoma susceptibility and oncogenic addiction to LMO1 (Oldridge et al., 2015). The G > T SNP was located within an intronic super-enhancer element of the *LMO1* gene. The tumorigenic "G" allele resides within a conserved GATA3 binding site and this allele was associated with an active super-enhancer state whereas the protective "T" allele disrupts GATA3 binding and is associated with significantly reduced super-enhancer activity and LMO1 expression. Alternatively, SNPs occurring in super-enhancers can also promote tumorigenesis by disrupting super-enhancer activity associated with tumor suppressor genes. In chronic lymphocytic leukemia, a SNP disrupts the binding of TF RELA to the super-enhancer linked with the pro-apoptotic BH3-only protein, BMF (Kandaswamy et al., 2016). This SNP was associated with decreased BMF expression, increased anti-apoptotic function of BCL2, thereby promoting tumorigenesis.

3.2. Hijacking of super-enhancers by 3D chromatin changes

Recent results from high resolution chromosome conformation capture methods suggest that the mammalian genomes are organized into a series of topologically associating domains (TADs) of average size of ~1 Mb (Dixon et al., 2012; Lieberman-Aiden et al., 2009; Rao et al., 2014; Sexton et al., 2012). Chromatin regions within a TAD on average interact with themselves more frequently than with regions outside the TAD. TAD structures are largely invariant across diverse cell types and are evolutionarily conserved across related species (Dixon,

Gorkin, & Ren, 2016), and are partitioned by regions displaying abrupt changes in the directionality of the interactions, which are defined as the boundary regions. It is now clear that one of the main functions of TADs is to constrain long range enhancer-promoter interactions within the TAD thereby insulating promoters from distal enhancers and super-enhancers located in the neighboring TADs (Dekker & Mirny, 2016; Dixon et al., 2016; Sexton & Cavalli, 2015). Naturally, either genetic or epigenetic disruption of TAD boundaries can result in aberrant enhancer/super-enhancers to promoter interactions forming new regulatory circuits (Furlong & Levine, 2018; Spielmann et al., 2018).

TAD structures are established through the binding of insulator CCCTC-binding factor (CTCF) in association with the cohesin complex at TAD boundaries (Nora et al., 2017; Rao et al., 2014; Zuin et al., 2014). Interestingly, most of these TAD boundaries are formed between pairs of CTCF binding sites in convergent (forward-reverse) orientation and this polarity of CTCF binding is critical for the directionality of loop formation (S. S. P. Rao et al., 2014). Inversion of CTCF binding sites can change the directionality of TAD interactions leading to altered regulatory space (de Wit et al., 2015; Guo et al., 2015). Collectively these reports supported the idea that these structural domains are the basic functional units of regulatory interactions and disruptions of these domains leading to inadvertent oncogene activation was soon reported in various cancer subtypes. In a primary report, Hnisz and colleagues identified recurrent microdeletions that eliminate the boundary sites of insulated neighborhoods containing prominent oncogenes involved in T-cell acute lymphoblastic leukemia pathogenesis (Hnisz et al., 2016). The authors were able to recapitulate some of these deletions in human embryonic kidney fibroblasts by CRISPR-mediated genome editing that led to new long range regulatory interactions and upregulation of proto-oncogenes *TAL1* and *LMO2* (Fig. 2c). A broader influence of TAD reorganization in oncogenic activation was shown by a pan-cancer analysis using a computational framework termed cis expression structural expression mapping (CESAM) to detect cancer related gene overexpression resulting from reorganization of TAD structures (Weischenfeldt et al., 2017). Amongst the top candidates identified, the authors characterized a TAD boundary deletion event that led to the spreading of active chromatin to the adjacent fused TAD and generation of a super-enhancer element, that can now increase the expression of *IRS4* gene in sarcoma and squamous cancer. In another example, a TAD was reorganized as a result of a tandem duplication event and was directly implicated in regulating *IGF2* gene expression in colorectal cancer. Specifically, tandem duplication of *IGF2* gene and a super-enhancer element in the adjoining TAD along with the intervening boundary region led to the formation of a neoTAD and upregulation of IGF2 expression (Weischenfeldt et al., 2017). Using CESAM and an independent framework that integrated optical mapping to high throughput chromosome conformation capture and whole genomic sequencing datasets, two recent reports identified many neoTADs and potential enhancer hijacking events in medulloblastoma and other cancer subtypes (Dixon et al., 2018; Northcott et al., 2017). These alterations targeted known driver genes like *PRDM6*, *ERBB2*, *ETV1*, *ETV4*, *MYC* and *TERT*. Further support for a prominent role of TAD boundary disruption in tumorigenesis is exemplified by recurrent mutations of CTCF and cohesin binding sites throughout multiple cancer subtypes (D. Hnisz et al., 2016; Katainen et al., 2015). Additionally, CTCF and members of the cohesin complex are frequently mutated in cancer (Kon et al., 2013; Lawrence et al., 2014; Taylor, Platt, Hurst, Thygesen, & Knowles, 2014). Moreover, CTCF and cohesin haploinsufficient mice are predisposed to cancer (Kemp et al., 2014; Mazumdar et al., 2015; Mullenders et al., 2015; Viny et al., 2015). However, it is still unclear how these mutations alter global or local regulatory interactions that may contribute to oncogenic transformation.

In addition to somatic mutations targeting TAD boundaries, epigenetic deregulation as a causal mechanism for TAD disruption has been demonstrated in gliomas harboring gain-of-function mutations in *IDH* genes (Flavahan et al., 2016). Mutant IDH cells accumulate the oncometabolite 2-hydroxyglutarate which, in turn, represses the TET family proteins (TET1–3) (Xu et al., 2011). TETs catalyze the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosines (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) in the genome, modifications considered to be key intermediates in the process of active DNA demethylation (Cimmino, Abdel-Wahab, Levine, & Aifantis, 2011). This leads to increased CpG methylation in IDH-mutant gliomas (Turcan et al., 2012). Since previous reports have correlated changes in binding of CTCF with differential DNA methylation (Bell & Felsenfeld, 2000; Hark et al., 2000; H. Wang et al., 2012), Flavahan and colleagues explored potential TAD disruption events and concomitant oncogene activation associated with increased methylation in IDH gliomas (Flavahan et al., 2016). In support of this hypothesis, partial disruption of a TAD structure was shown as a result of increased methylation in the CTCF site and reduced CTCF binding that led to the activation of oncogenic driver, PDGFRA, by enhancers located outside the normal TAD of *PDGFRA* (Fig. 2c).

Super-enhancers are frequently enriched near the recently described stripe anchor domains that are formed when cohesin loading takes place near a CTCF anchor motif (Vian et al., 2018). Based on the current widely accepted loop extrusion model of loop formation, as DNA is extruded through cohesin rings, one extrusion subunit near the CTCF anchor site might get arrested while the other unit continues to slide along the chromatin (Fudenberg et al., 2016; Ganji et al., 2018; Sanborn et al., 2015). This leads to a continuous transient interaction of the arrested loop anchor with entire TAD domains at high frequency. These stripe anchors often tether super-enhancers to cognate promoters and are associated with strong TAD boundaries and elevated CTCF binding near these anchor points (Vian et al., 2018). In support of a potential role for stripe anchors in upregulating super-enhancer-mediated target gene expression in cancers, strong TAD boundaries associated with increased CTCF binding were found to be frequently co-duplicated with nearby super-enhancers in cancer patients (Gong et al., 2018).

4. The MYC "enhancer-ome" - a paradigm for tumor development

The *MYC* oncogene is at the crossroads of many important biological pathways and processes associated with neoplastic cell growth and proliferation. Expression of MYC is elevated or deregulated in up to 70% of human cancers and has been acknowledged contributing to the genesis of many human cancers (Dang, 2012). Given this, MYC expression is tightly controlled at the transcriptional, post-transcriptional, translational and the post translational level (Dang, 2012). The *MYC* proto-oncogene itself is under tight transcriptional control by nearby regulatory enhancers and super-enhancers, which not surprisingly are frequently deregulated in cancers. In fact, the first molecular evidence indicating that changes in regulatory DNA sequences can cause cancer was discovered in Burkitt lymphoma cells that had recurrent translocations of the *MYC* oncogene close to the enhancer region of the immunoglobulin heavy chain (IGH) locus (ar-Rushdi et al., 1983; Dalla-Favera et al., 1982; Erikson, ar-Rushdi, Drwinga, Nowell, & Croce, 1983; Taub et al., 1982). Following this initial finding, the MYC regulatory landscape has been under intense investigation in several cancers.

MYC is located within a 2 Mb "gene desert" on chromosome 8q24 surrounded by several cell type specific enhancer/super-enhancers that regulate MYC expression in different cancer subtypes (Lancho & Herranz, 2018) (Fig. 3). For example, in T-ALL, the MYC locus is controlled by distant 3D interactions with a super-enhancer element approximately 1 .4Mb apart from the *MYC* promoter (Herranz et al., 2014; Yashiro-Ohtani et al., 2014). This super-enhancer element named N-Me/NDME was focally amplified in several T-ALL samples and was bound by TF, NOTCH1, a key oncogenic driver in T-ALL. Further 3C experiments confirmed interactions of the MYC promoter with N-

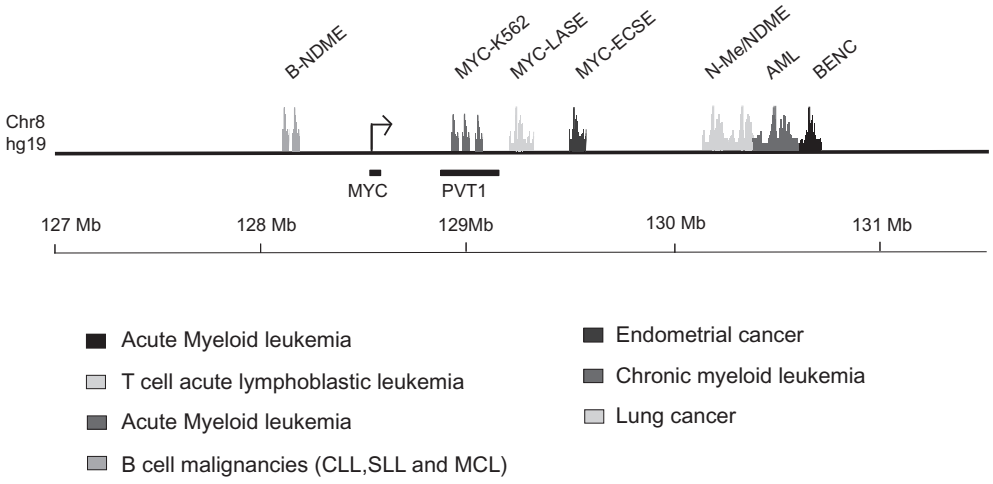

Fig. 3. Graphical representation of super-enhancers regulating MYC expression in different cancer subtypes.

Me. Additionally, in support of an oncogenic role for N-Me, T-cell specific deletion of N-Me prevented the transformation of T cells in a NOTCH1-driven *in vivo* tumor model (Herranz et al., 2014; Yashiro-Ohtani et al., 2014). A role for NOTCH1-activated super-enhancers regulating MYC expression was also identified in B cell malignancies including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) (Fabbri et al., 2017; Ryan et al., 2017). Unlike the T-ALL specific N-Me/NDME, the NOTCH1-bound enhancers in CLL and MCL were located 5′ to MYC and were referred as B-cell NOTCH dependent *MYC* enhancer (B-NDME). Distal to the N-Me/NDME, another super-enhancer cluster named BDME/BENC was shown to regulate MYC expression during normal hematopoiesis and AML pathogenesis (Bahr et al., 2018; Shi et al., 2013). To investigate regulatory regions implicated in MYC expression in CML, a functional screen was performed using CRISPR interference (CRISPRi) using a tiling array (Fulco et al., 2016). CRISPRi couples the programmable properties of catalytically dead Cas9 and a fused KRAB repressor domain to alter the chromatin state around target locus. A tiling CRISPRi screen targeting a 1 .2Mb window surrounding the *MYC* oncogene in CML cell line K562 led to the identification of a cluster of putative enhancer elements whose transcriptional silencing led to reduced MYC expression and proliferation.

Furthermore, somatic copy number analysis across 29 tumor subtypes led to the identification of focal amplifications of distinct super-enhancer elements downstream of MYC specific to lung adenocarcinoma (*MYC*-LASE) and endometrial carcinoma (*MYC*-ECSE) (Zhang et al., 2016). In further support of a cell type specific role for these super-enhancer elements, CRISPR/Cas9-mediated repression or deletion of LASE regions reduced expression of MYC in lung adenocarcinoma cells but not in control human embryonic kidney cells. Additionally, chromatin accessibility landscape determined across 23 cancer types identified several potential regulatory clusters both 5′ and 3′ of the MYC oncogene (Corces et al., 2018). Also, several genome-wide association studies, identified SNPs associated with increased risk to many cancers including colon, breast and prostate in tissue specific enhancer clusters regulating MYC (Ahmadiyeh et al., 2010; Jia et al., 2009; Pomerantz et al., 2009; Sotelo et al., 2010; Tuupanen et al., 2009; Wasserman, Aneas, & Nobrega, 2010). These SNPs can alter binding of TFs, such as TCF and FOXA1, with consequences on the enhancer-promoter looping and expression of MYC in tissue and allele specific way. *In vivo* mouse models harboring deletions of MYC super-enhancer elements are resistant to the development of intestinal and mammary tumors, supporting the notion of targeting MYC super-enhancer activity as a promising therapeutic strategy in MYC dependent cancers (Dave et al., 2017; Sur et al., 2012). For a more comprehensive regulation of MYC in cancers by enhancers and super-enhancers, see (Lancho & Herranz, 2018).

5. Pharmacological targeting of super-enhancer addiction in cancers

Genetic alterations targeting super-enhancers lead to dysregulated transcriptional programs in cancers. Cancer cells can become highly addicted to these transcriptional programs providing super-enhancers as novel targets for therapeutic interventions. In addition, a strong rationale for targeting super-enhancers in cancer also comes from the notion that driver oncogenic mutations hack into resident pre-configured super-enhancer regenerative programs of the target tissue to initiate and sustain oncogenic transcriptional programs (Evan et al., 2017). Support to this view stems from the observation that oncogenes Ras and MYC co-operate to induce tumors across several tissues and that these tumors usually display tissue specific phenotypes of spontaneous cancers in these tissues. These observations further strengthen the rationale that interfering with super-enhancer networks should disrupt tumorigenic programs across different tissue and cancer subtypes. Amongst the current class of small molecule inhibitors targeting super-enhancers, BET inhibitors (BETi), a competitive inhibitor of bromodomain and extraterminal (BET) family proteins (BRD2, BRD3, BRD4 and BRDT) and inhibitors of cyclin dependent kinases, particularly CDK7 and CDK9, have been potent in selectively killing cancer cells by inhibiting super-enhancer driven oncogenic transcription. The rationale behind using these small molecule inhibitors and their mechanisms of action are discussed below.

Transcription is a multistep process that involves recruitment of the RNA polymerase to appropriate promoters leading to transcription initiation followed by promoter proximal pausing and final transition into productive elongation. Sites of active super-enhancer associated transcription are enriched for H3K27ac mark regions. This active chromatin mark is recognized by (BET) family member BRD4. BRD4 interacts with the Mediator co-activator complex leading to the stepwise recruitment of the CDK7-containing TFIIH initiation complex and the CDK9-containing p-TEFb elongation complex. CDK7 and CDK9 control the dynamics of transcriptional initiation, pause release and elongation by catalyzing regulatory phosphorylation of the carboxy terminal domain (CTD) of RNA pol II (Allen & Taatjes, 2015; Jonkers & Lis, 2015). CDK7 dependent phosphorylation of RNA pol II CTD at Ser-5 and Ser-7 initiates transcription and plays an active role in promoter proximal pausing by enabling the loading of negative elongation factor (NELF) and DRB-sensitivity-inducing factor (DSIF). Release from proximal pausing and transition to productive elongation is mediated by CDK9-mediated Ser-2 phosphorylation of RNA pol II CTD that recruit elongation factor, pTEFB (Eick & Geyer, 2013; Zhou, Li, & Price, 2012). Thus, BRD4, Mediator complex and transcriptional CDKs, considered core regulators of transcription, have emerged as attractive targets for impeding oncogenic transcription in the last decade.

5.1. Inhibitors of BET family proteins

BETi competitively inhibits binding of BET bromodomains to acetyllysines displacing BET-containing protein complexes from chromatin (Filippakopoulos et al., 2010; Nicodeme et al., 2010). Two initial reports demonstrated BETi (I-BET151 and JQ1) induce strong suppression of tumor progression in pre-clinical models of acute myeloid leukemia (AML) and multiple myeloma (Delmore et al., 2011; Zuber et al., 2011). This strong therapeutic effect was mediated by the suppression of MYC levels and its downstream transcriptional program. Following these initial reports, BETi were reported to selectively downregulate MYC expression in various tumor models including neuroblastoma, medulloblastoma, MLL-rearranged acute leukemia, Burkitt lymphoma and acute lymphoblastic leukemia (ALL) (Bandopadhayay et al., 2014; Dawson et al., 2011; King et al., 2013; Knoechel et al., 2014; Mertz et al., 2011; Puissant et al., 2013). Since BRD4 is reported to be the dominant transcriptional regulator amongst the BET family proteins, most studies linked the therapeutic effects of BETi to BRD4 inhibition (Zuber et al., 2011). Insights into the disease relevant functions of BRD4 were obtained from genome-wide profiling of BRD4 occupancy by chromatin immunoprecipitation. Examination of BRD4 occupancy at genes whose transcription is particularly sensitive to BETi led to the finding that BETi-sensitive genes are often associated with nearby super-enhancers that exhibit high levels of BRD4 occupancy and are associated with acute loss of BRD4 binding following BETi treatment (Chapuy et al., 2013; Loven et al., 2013). Recent evidence using AML cell lines indicate that only a minority of super-enhancers are sensitive to BETi treatment and these super-enhancers in addition to eviction of BRD4 are associated with dramatic loss of Mediator binding (Bhagwat et al., 2016). In addition, TFs, YAP and TAZ, were shown to be essential for the recruitment of BRD4 to super-enhancers, as well as a preferential loss of BRD4 and sensitivity to JQ1 treatment amongst YAP/TAZ occupied enhancers and super-enhancers compared to enhancers and super-enhancers without YAP/TAZ binding sites (Zanconato et al., 2018). These reports suggest further understanding of the mechanism underlying this differential sensitivity of super-enhancers to BETi can help to streamline potential use of BETi in the clinic.

5.2. Inhibitors of transcriptional CDKs

Inhibitors of cyclin-dependent kinases, CDK7 and CDK9, have recently emerged as strong candidates for targeting oncogenic super-enhancers. THZ1, a covalent inhibitor of CDK7, completely abrogated CDK7-dependent phosphorylation of RNA pol II CTD at Ser-5 and Ser-7 that promotes transcriptional initiation (Kwiatkowski et al., 2014). This was also accompanied by the loss of CDK9-mediated Ser-2 phosphorylation, a marker of transcriptional elongation. CDK7 inhibition by THZ1 is associated with global transcriptional downregulation at high doses, but cancer cell lines were sensitive to lower doses of THZ1. Using T-ALL as a model system, it was initially shown that sensitivity to THZ1 is conferred by the targeting of super-enhancer driving RUNX1. Further reports demonstrated that THZ1 can selectively target super-enhancer driven transcriptional programs, including MYC-dependent transcriptional amplification and expression of other cancer-specific oncogenic TFs and signaling molecules. THZ1 treatment led to sustained tumor growth inhibition in *in vitro* cell lines and *in vivo* pre-clinical xenograft models of small cell lung cancer, MYCN amplified neuroblastoma and triple negative breast cancer (Chipumuro et al., 2014; Christensen et al., 2014; Y. Wang et al., 2015). Additionally, small molecule co-inhibitors of CKIα and CDK7/9 showed strong efficacy in AML preclinical models (Minzel et al., 2018). These inhibitors couple p53 activation associated with CKIα inhibition with the suppression of super-enhancer driven oncogenes by CDK7/9 inhibition. Although the mechanism accounting for MYC specificity to CDK7 and BRD4 inhibition requires further investigation, inhibiting super-enhancer-associated transcriptional regulators provides a novel platform for single-agent targeting of multiple oncogenes.

5.3. Resistance to BET and CDK inhibitors

On the downside, like all other cancer monotherapies, resistance to single agent treatment of BETi and THZ1 has been reported in pre-clinical models. Resistance to BET inhibitors is primarily mediated by global alterations in gene expression that compensates for the effects of BET inhibition (Fong et al., 2015; Rathert et al., 2015). In MLL-fusion AML, resistance to BETi is dependent on the activation of WNT signaling pathway that restores MYC expression and overrides the BETi mediated downregulation of MYC expression (Fong et al., 2015; Rathert et al., 2015). In the case of Triple Negative breast cancers, resistance to BETi was achieved through increased interaction with mediator complex protein MED1 and resultant bromodomain independent recruitment to chromatin (Shu et al., 2016). This MED1-BRD4 interaction was mediated by hyperphosphorylation of BRD4 attributed to the decreased activity of phosphatase PP2A. Resistance to transcriptional CDK inhibitor THZ1 is primarily reported to be mediated by drug pump activation by upregulation of multidrug transporters ABCB1 and ABCG2 in neuroblastoma (Gao et al., 2018). Overall these reports highlight the importance of using inhibitors targeting super-enhancer biology in combination with other drugs to have synergistic effects and to reduce development of resistance mechanisms. In support of this, successful combination of BETi with gamma secretase inhibitors of NOTCH1 activation and PI3K inhibitors have been reported in mouse models of T-ALL and breast cancer respectively (Knoechel et al., 2014; Stratikopoulos et al., 2015).

5.4. Super-enhancer profiling for future precision therapies

In addition to targeting the core transcriptional regulators, several new studies have mapped active chromatin landscapes in multiple cancers with the goal of identifying essential super-enhancer genes and the underlying core transcriptional networks for therapeutic targeting (Cohen et al., 2017; Ke et al., 2017; Mack et al., 2017; McKeown et al., 2017; Ooi et al., 2016). As a proof of principle, targeting these core transcriptional networks, either by small-molecule inhibitors or knockdown by RNA interference, diminished tumor growth in both *in vitro* and *in vivo* models (Mack et al., 2017; McKeown et al., 2017). Super-enhancer profiling of AML patients led to the identification of six novel subgroups, one of which was defined by strong super-enhancer activity at the retinoic acid receptor alpha gene locus (RARα). This subgroup was particularly sensitive to RARα agonist that induced differentiation and loss of proliferation (McKeown et al., 2017). In support of a broad role for enhancer reprogramming in tumorigenesis and tumor evolution, a recent study reported metastatic progression in pancreatic cancer to be associated with widespread and recurrent changes in enhancer landscape. These changes were mediated by transcription factor FOXA1 and results in the activation of a transcriptional program specific of a more primitive, developmentally plastic early endodermal stem cell state (Roe et al., 2017). Thus, super-enhancer profiling to identify core regulatory circuits can implicate future targeted therapy across the different stages of cancer (Boeva et al., 2017; van Groningen et al., 2017).

6. Concluding remarks

Research in the last decade has established the basic concepts of super-enhancer biology and their role in tumorigenesis. So far, it is clear that oncogenic super-enhancers are present in multiple cancer subtypes and are essential for the maintenance of cancer cell identity. Super-enhancers drive the expression of key oncogenes and confer tumor dependencies which, ultimately, has provided a framework for target discovery in cancers that lack clear known genetic drivers. It is also clear that structural and epigenetic changes which can alter 3D organization can result in super-enhancer hijacking and inadvertent

activation of oncogenes. This further suggests that super-enhancers have to be studied in the context of 3D chromatin organization to get a complete picture of their role in tumorigenesis. From the therapeutic standpoint, since the essential components of the super-enhancers are common in different cancer subtypes, targeting individual components of super-enhancers like BRD4, CDK7 or CDK9 has shown great promise in multiple pre-clinical tumor models. With this in mind, future research should aim to further elucidate how individual components of super-enhancers regulate super-enhancer function. These insights, along with a greater understanding of phase separation in super-enhancer assembly and activation, may shed light on how oncogenic signaling impacts super-enhancer assembly and function leading to the identification of novel candidates for targeting super-enhancer in cancers.

Conflict of interest statement

The author declares that there is no conflict of interest.

Acknowledgments

The author acknowledges Drs. Andreas Kloetgen, Charalampos Lazaris and Matthew Witkowski for critical reading of the manuscript and helpful discussions. P.T. is supported by AACR-Incyte Leukemia Research fellowship.

References

Ahmadiyeh, N., Pomerantz, M. M., Grisanzio, C., Herman, P., Jia, L., Almendro, V., ... Freedman, M. L. (2010). 8q24 prostate, breast, and colon cancer risk loci show tissue-specific long-range interaction with MYC. *Proceedings of the National Academy of Sciences of the United States of America 107*(21), 9742–9746. https://doi.org/10.1073/pnas.0910668107.

Allen, B. L., & Taatjes, D. J. (2015). The mediator complex: A central integrator of transcription. *Nature Reviews. Molecular Cell Biology 16*(3), 155–166. https://doi.org/10.1038/nrm3951.

ar-Rushdi, A., Nishikura, K., Erikson, J., Watt, R., Rovera, G., & Croce, C. M. (1983). Differential expression of the translocated and the untranslocated c-myc oncogene in Burkitt lymphoma. *Science 222*(4622), 390–393.

Bahr, C., von Paleske, L., Uslu, V. V., Remeseiro, S., Takayama, N., Ng, S. W., ... Spitz, F. (2018). A Myc enhancer cluster regulates normal and leukaemic haematopoietic stem cell hierarchies. *Nature 553*(7689), 515–520. https://doi.org/10.1038/nature25193.

Banani, S. F., Lee, H. O., Hyman, A. A., & Rosen, M. K. (2017). Biomolecular condensates: Organizers of cellular biochemistry. *Nature Reviews. Molecular Cell Biology 18*(5), 285–298. https://doi.org/10.1038/nrm.2017.7.

Bandopadhayay, P., Bergthold, G., Nguyen, B., Schubert, S., Gholamin, S., Tang, Y., ... Cho, Y. -J. (2014). BET bromodomain inhibition of MYC-amplified medulloblastoma. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 20*(4), 912–925. https://doi.org/10.1158/1078-0432.CCR-13-2281.

Bell, A. C., & Felsenfeld, G. (2000). Methylation of a CTCF-dependent boundary controls imprinted expression of the Igf2 gene. *Nature 405*, 482. https://doi.org/10.1038/35013100.

Bergeron-Sandoval, L. P., Safaee, N., & Michnick, S. W. (2016). Mechanisms and consequences of macromolecular phase separation. *Cell 165*(5), 1067–1079. https://doi.org/10.1016/j.cell.2016.05.026.

Bhagwat, A. S., Roe, J. -S., Mok, B. Y. L., Hohmann, A. F., Shi, J., & Vakoc, C. R. (2016). BET Bromodomain inhibition releases the mediator complex from select cis-regulatory elements. *Cell Reports 15*(3), 519–530. https://doi.org/10.1016/j.celrep.2016.03.054.

Boeva, V., Louis-Brennetot, C., Peltier, A., Durand, S., Pierre-Eugène, C., Raynal, V., ... Janoueix-Lerosey, I. (2017). Heterogeneity of neuroblastoma cell identity defined by transcriptional circuitries. *Nature Genetics 49*, 1408. https://doi.org/10.1038/ng.3921https://www.nature.com/articles/ng.3921 (supplementary-information).

Boija, A., Klein, I. A., Sabari, B. R., Dall'Agnese, A., Coffey, E. L., Zamudio, A. V., ... Young, R. A. (2018). Transcription factors activate genes through the phase-separation capacity of their activation domains. *Cell*. https://doi.org/10.1016/j.cell.2018.10.042.

Bradner, J. E., Hnisz, D., & Young, R. A. (2017). Transcriptional addiction in cancer. *Cell 168*(4), 629–643. https://doi.org/10.1016/j.cell.2016.12.013.

Brangwynne, C. P., Eckmann, C. R., Courson, D. S., Rybarska, A., Hoege, C., Gharakhani, J., ... Hyman, A. A. (2009). Germline P granules are liquid droplets that localize by controlled dissolution/condensation. *Science 324*(5935), 1729–1732. https://doi.org/10.1126/science.1172046.

Brown, J. D., Lin, C. Y., Duan, Q., Griffin, G., Federation, A., Paranal, R. M., ... Plutzky, J. (2014). NF-kappaB directs dynamic super enhancer formation in inflammation and atherogenesis. *Molecular Cell 56*(2), 219–231. https://doi.org/10.1016/j.molcel.2014.08.024.

Bulger, M., & Groudine, M. (2011). Functional and mechanistic diversity of distal transcription enhancers. *Cell 144*(3), 327–339. https://doi.org/10.1016/j.cell.2011.01.024.

Calo, E., & Wysocka, J. (2013). Modification of enhancer chromatin: What, how, and why? *Molecular Cell 49*(5), 825–837. https://doi.org/10.1016/j.molcel.2013.01.038.

Chapuy, B., McKeown, M. R., Lin, C. Y., Monti, S., Roemer, M. G. M., Qi, J., ... Bradner, J. E. (2013). Discovery and characterization of super-enhancer-associated dependencies in diffuse large B cell lymphoma. *Cancer Cell 24*(6), 777–790. https://doi.org/10.1016/j.ccr.2013.11.003.

Chen, H., Levo, M., Barinov, L., Fujioka, M., Jaynes, J. B., & Gregor, T. (2018). Dynamic interplay between enhancer-promoter topology and gene activity. *Nature Genetics 50*(9), 1296–1303. https://doi.org/10.1038/s41588-018-0175-z.

Chipumuro, E., Marco, E., Christensen, C. L., Kwiatkowski, N., Zhang, T., Hatheway, C. M., ... George, R. E. (2014). CDK7 inhibition suppresses super-enhancer-linked oncogenic transcription in MYCN-driven cancer. *Cell 159*(5), 1126–1139. https://doi.org/10.1016/j.cell.2014.10.024.

Christensen, C. L., Kwiatkowski, N., Abraham, B. J., Carretero, J., Al-Shahrour, F., Zhang, T., ... Wong, K. -K. (2014). Targeting transcriptional addictions in small cell lung cancer with a covalent CDK7 inhibitor. *Cancer Cell 26*(6), 909–922. https://doi.org/10.1016/j.ccell.2014.10.019.

Cimmino, L., Abdel-Wahab, O., Levine, R. L., & Aifantis, I. (2011). TET family proteins and their role in stem cell differentiation and transformation. *Cell Stem Cell 9*(3), 193–204. https://doi.org/10.1016/j.stem.2011.08.007.

Cohen, A. J., Saiakhova, A., Corradin, O., Luppino, J. M., Lovrenert, K., Bartels, C. F., ... Scacheri, P. C. (2017). Hotspots of aberrant enhancer activity punctuate the colorectal cancer epigenome. *Nature Communications 8*, 14400. https://doi.org/10.1038/ncomms14400https://www.nature.com/articles/ncomms14400 (supplementary-information).

Consortium, T. E. P., Dunham, I., Kundaje, A., Aldred, S. F., Collins, P. J., Davis, C. A., ... Birney, E. (2012). An integrated encyclopedia of DNA elements in the human genome. *Nature 489*, 57. https://doi.org/10.1038/nature11247https://www.nature.com/articles/nature11247 (supplementary-information).

Corces, M. R., Granja, J. M., Shams, S., Louie, B. H., Seoane, J. A., Zhou, W., ... Chang, H. Y. (2018). The chromatin accessibility landscape of primary human cancers. *Science 362*(6413). https://doi.org/10.1126/science.aav1898.

Creyghton, M. P., Cheng, A. W., Welstead, G. G., Kooistra, T., Carey, B. W., Steine, E. J., ... Jaenisch, R. (2010). Histone H3K27ac separates active from poised enhancers and predicts developmental state. *Proceedings of the National Academy of Sciences of the United States of America 107*(50), 21931–21936. https://doi.org/10.1073/pnas.1016071107.

Dalla-Favera, R., Bregni, M., Erikson, J., Patterson, D., Gallo, R. C., & Croce, C. M. (1982). Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. *Proceedings of the National Academy of Sciences of the United States of America 79*(24), 7824–7827.

Dang, C. V. (2012). MYC on the path to cancer. *Cell 149*(1), 22–35. https://doi.org/10.1016/j.cell.2012.03.003.

Dave, K., Sur, I., Yan, J., Zhang, J., Kaasinen, E., Zhong, F., ... Taipale, J. (2017). Mice deficient of Myc super-enhancer region reveal differential control mechanism between normal and pathological growth. *eLife 6*, e23382. https://doi.org/10.7554/eLife.23382.

Dawson, M. A., Prinjha, R. K., Dittmann, A., Giotopoulos, G., Bantscheff, M., Chan, W. -I., ... Kouzarides, T. (2011). Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. *Nature 478*, 529. https://doi.org/10.1038/nature10509https://www.nature.com/articles/nature10509 (supplementary-information).

Dekker, J., & Mirny, L. (2016). The 3D genome as moderator of chromosomal communication. *Cell 164*(6), 1110–1121. https://doi.org/10.1016/j.cell.2016.02.007.

Delmore, J. E., Issa, G. C., Lemieux, M. E., Rahl, P. B., Shi, J., Jacobs, H. M., ... Mitsiades, C. S. (2011). BET Bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell 146*(6), 904–917. https://doi.org/10.1016/j.cell.2011.08.017.

Deng, W., Lee, J., Wang, H., Miller, J., Reik, A., Gregory, P. D., ... Blobel, G. A. (2012). Controlling long-range genomic interactions at a native locus by targeted tethering of a looping factor. *Cell 149*(6), 1233–1244. https://doi.org/10.1016/j.cell.2012.03.051.

Dixon, J. R., Gorkin, D. U., & Ren, B. (2016). Chromatin domains: The unit of chromosome organization. *Molecular Cell 62*(5), 668–680. https://doi.org/10.1016/j.molcel.2016.05.018.

Dixon, J. R., Selvaraj, S., Yue, F., Kim, A., Li, Y., & Shen, Y. (2012). Topological domains in mammalian genomes identified by analysis of chromatin interactions. *Nature*, 485. https://doi.org/10.1038/nature11082.

Dixon, J. R., Xu, J., Dileep, V., Zhan, Y., Song, F., Le, V. T., ... Yue, F. (2018). Integrative detection and analysis of structural variation in cancer genomes. *Nature Genetics 50*(10), 1388–1398. https://doi.org/10.1038/s41588-018-0195-8.

Drier, Y., Cotton, M. J., Williamson, K. E., Gillespie, S. M., Ryan, R. J., Kluk, M. J., ... Bernstein, B. E. (2016). An oncogenic MYB feedback loop drives alternate cell fates in adenoid cystic carcinoma. *Nature Genetics 48*(3), 265–272. https://doi.org/10.1038/ng.3502.

Eick, D., & Geyer, M. (2013). The RNA polymerase II Carboxy-terminal domain (CTD) code. *Chemical Reviews 113*(11), 8456–8490. https://doi.org/10.1021/cr400071f.

Erikson, J., ar-Rushdi, A., Drwinga, H. L., Nowell, P. C., & Croce, C. M. (1983). Transcriptional activation of the translocated c-myc oncogene in burkitt lymphoma. *Proceedings of the National Academy of Sciences of the United States of America 80*(3), 820–824.

Evan, G. I., Hah, N., Littlewood, T. D., Sodir, N. M., Campos, T., Downes, M., & Evans, R. M. (2017). Re-engineering the pancreas tumor microenvironment: A "regenerative program" hacked. *Clinical Cancer Research 23*(7), 1647–1655. https://doi.org/10.1158/1078-0432.ccr-16-3275.

Fabbri, G., Holmes, A. B., Viganotti, M., Scuoppo, C., Belver, L., Herranz, D., ... Dalla-Favera, R. (2017). Common nonmutational NOTCH1 activation in chronic lymphocytic leukemia. *Proceedings of the National Academy of Sciences of the United States of America 114*(14), E2911–e2919. https://doi.org/10.1073/pnas.1702564114.

Filippakopoulos, P., Qi, J., Picaud, S., Shen, Y., Smith, W. B., Fedorov, O., ... Bradner, J. E. (2010). Selective inhibition of BET bromodomains. *Nature 468*(7327), 1067–1073. https://doi.org/10.1038/nature09504.

Flavahan, W. A., Drier, Y., Liau, B. B., Gillespie, S. M., Venteicher, A. S., Stemmer-Rachamimov, A. O., ... Bernstein, B. E. (2016). Insulator dysfunction and oncogene activation in IDH mutant gliomas. *Nature 529*(7584), 110–114. https://doi.org/10.1038/nature16490.

Fong, C. Y., Gilan, O., Lam, E. Y. N., Rubin, A. F., Ftouni, S., Tyler, D., ... Dawson, M. A. (2015). BET inhibitor resistance emerges from leukaemia stem cells. *Nature 525*, 538. https://doi.org/10.1038/nature14888https://www.nature.com/articles/nature14888 (supplementary-information).

Fudenberg, G., Imakaev, M., Lu, C., Goloborodko, A., Abdennur, N., & Mirny, L. A. (2016). Formation of chromosomal domains by loop extrusion. *Cell Reports 15*(9), 2038–2049. https://doi.org/10.1016/j.celrep.2016.04.085.

Fulco, C. P., Munschauer, M., Anyoha, R., Munson, G., Grossman, S. R., Perez, E. M., ... Engreitz, J. M. (2016). Systematic mapping of functional enhancer-promoter connections with CRISPR interference. *Science*. https://doi.org/10.1126/science.aag2445.

Furlong, E. E. M., & Levine, M. (2018). Developmental enhancers and chromosome topology. *Science 361*(6409), 1341–1345. https://doi.org/10.1126/science.aau0320.

Ganji, M., Shaltiel, I. A., Bisht, S., Kim, E., Kalichava, A., Haering, C. H., & Dekker, C. (2018). Real-time imaging of DNA loop extrusion by condensin. *Science 360*(6384), 102–105. https://doi.org/10.1126/science.aar7831.

Gao, Y., Zhang, T., Terai, H., Ficarro, S. B., Kwiatkowski, N., Hao, M. -F., ... George, R. E. (2018). Overcoming resistance to the THZ series of covalent transcriptional CDK inhibitors. *Cell Chemical Biology 25*(2), 135–142 (e135) https://doi.org/10.1016/j.chembiol.2017.11.007.

Glodzik, D., Morganella, S., Davies, H., Simpson, P. T., Li, Y., Zou, X., ... Nik-Zainal, S. (2017). A somatic-mutational process recurrently duplicates germline susceptibility loci and tissue-specific super-enhancers in breast cancers. *Nature Genetics 49*, 341. https://doi.org/10.1038/ng.3771https://www.nature.com/articles/ng.3771 (supplementary-information).

Gong, Y., Lazaris, C., Sakellaropoulos, T., Lozano, A., Kambadur, P., Ntziachristos, P., ... Tsirigos, A. (2018). Stratification of TAD boundaries reveals preferential insulation of super-enhancers by strong boundaries. *Nature Communications 9*(1), 542. https://doi.org/10.1038/s41467-018-03017-1.

van Groningen, T., Koster, J., Valentijn, L. J., Zwijnenburg, D. A., Akogul, N., Hasselt, N. E., ... Versteeg, R. (2017). Neuroblastoma is composed of two super-enhancer-associated differentiation states. *Nature Genetics 49*, 1261. https://doi.org/10.1038/ng.3899https://www.nature.com/articles/ng.3899 (supplementary-information).

Groschel, S., Sanders, M. A., Hoogenboezem, R., de Wit, E., Bouwman, B. A. M., Erpelinck, C. , ... Delwel, R. (2014). A single oncogenic enhancer rearrangement causes concomitant EVI1 and GATA2 deregulation in leukemia. *Cell 157*(2), 369–381. https://doi.org/10.1016/j.cell.2014.02.019.

Gross, D. S., & Garrard, W. T. (1988). Nuclease hypersensitive sites in chromatin. *Annual Review of Biochemistry 57*, 159–197. https://doi.org/10.1146/annurev.bi.57.070188.001111.

Guo, Y., Xu, Q., Canzio, D., Shou, J., Li, J., Gorkin, D. U., ... Wu, Q. (2015). CRISPR inversion of CTCF sites alters genome topology and enhancer/promoter function. *Cell 162*(4), 900–910. https://doi.org/10.1016/j.cell.2015.07.038.

Hark, A. T., Schoenherr, C. J., Katz, D. J., Ingram, R. S., Levorse, J. M., & Tilghman, S. M. (2000). CTCF mediates methylation-sensitive enhancer-blocking activity at the H19/Igf2 locus. *Nature 405*, 486. https://doi.org/10.1038/35013106.

Hay, D., Hughes, J. R., Babbs, C., Davies, J. O. J., Graham, B. J., Hanssen, L., ... Higgs, D. R. (2016). Genetic dissection of the alpha-globin super-enhancer in vivo. *Nature Genetics 48*(8), 895–903. https://doi.org/10.1038/ng.3605.

Heintzman, N. D., Stuart, R. K., Hon, G., Fu, Y., Ching, C. W., Hawkins, R. D., ... Ren, B. (2007). Distinct and predictive chromatin signatures of transcriptional promoters and enhancers in the human genome. *Nature Genetics 39*(3), 311–318. https://doi.org/10.1038/ng1966.

Herranz, D., Ambesi-Impiombato, A., Palomero, T., Schnell, S. A., Belver, L., Wendorff, A. A., ... Ferrando, A. A. (2014). A NOTCH1-driven MYC enhancer promotes T cell development, transformation and acute lymphoblastic leukemia. *Nature Medicine 20*(10), 1130–1137. https://doi.org/10.1038/nm.3665http://www.nature.com/nm/journal/v20/n10/abs/nm.3665.html (supplementary-information).

Hnisz, D., Abraham, B. J., Lee, T. I., Lau, A., Saint-Andre, V., Sigova, A. A., ... Young, R. A. (2013). Super-enhancers in the control of cell identity and disease. *Cell 155*(4), 934–947. https://doi.org/10.1016/j.cell.2013.09.053.

Hnisz, D., Schuijers, J., Lin, C. Y., Weintraub, A. S., Abraham, B. J., Lee, T. I., ... Young, R. A. (2015). Convergence of developmental and oncogenic signaling pathways at transcriptional super-enhancers. *Molecular Cell 58*(2), 362–370. https://doi.org/10.1016/j.molcel.2015.02.014.

Hnisz, D., Shrinivas, K., Young, R. A., Chakraborty, A. K., & Sharp, P. A. (2017). A phase separation model for transcriptional control. *Cell 169*(1), 13–23. https://doi.org/10.1016/j.cell.2017.02.007.

Hnisz, D., Weintraub, A. S., Day, D. S., Valton, A. L., Bak, R. O., Li, C. H., ... Young, R. A. (2016). Activation of proto-oncogenes by disruption of chromosome neighborhoods. *Science 351*(6280), 1454–1458. https://doi.org/10.1126/science.aad9024.

Jia, L., Landan, G., Pomerantz, M., Jaschek, R., Herman, P., Reich, D., ... Coetzee, G. A. (2009). Functional enhancers at the gene-poor 8q24 cancer-linked locus. *PLoS Genetics 5*(8), e1000597. https://doi.org/10.1371/journal.pgen.1000597.

Jonkers, I., & Lis, J. T. (2015). Getting up to speed with transcription elongation by RNA polymerase II. *Nature Reviews Molecular Cell Biology 16*, 167. https://doi.org/10.1038/nrm3953.

Kagey, M. H., Newman, J. J., Bilodeau, S., Zhan, Y., Orlando, D. A., van Berkum, N. L., ... Young, R. A. (2010). Mediator and cohesin connect gene expression and chromatin architecture. *Nature 467*, 430. https://doi.org/10.1038/nature09380https://www.nature.com/articles/nature09380 (supplementary-information).

Kandaswamy, R., Sava, G. P., Speedy, H. E., Bea, S., Martin-Subero, J. I., Studd, J. B., ... Houlston, R. S. (2016). Genetic predisposition to chronic lymphocytic leukemia is mediated by a BMF super-enhancer polymorphism. *Cell Reports 16*(8), 2061–2067. https://doi.org/10.1016/j.celrep.2016.07.053.

Katainen, R., Dave, K., Pitkänen, E., Palin, K., Kivioja, T., Välimäki, N., ... Aaltonen, L. A. (2015). *CTCF/cohesin-binding sites are frequently mutated in cancer. Vol. 47*. (pp. 818), 818. https://doi.org/10.1038/ng.3335https://www.nature.com/articles/ng.3335 (supplementary-information).

Ke, L., Zhou, H., Wang, C., Xiong, G., Xiang, Y., Ling, Y., ... Zhao, B. (2017). Nasopharyngeal carcinoma super-enhancer–driven ETV6 correlates with prognosis. *Proceedings of the National Academy of Sciences 114*(36), 9683–9688. https://doi.org/10.1073/pnas.1705236114.

Kemp, C. J., Moore, J. M., Moser, R., Bernard, B., Teater, M., Smith, L. E., ... Filippova, G. N. (2014). CTCF haploinsufficiency destabilizes DNA methylation and predisposes to cancer. *Cell Reports 7*(4), 1020–1029. https://doi.org/10.1016/j.celrep.2014.04.004.

King, B., Trimarchi, T., Reavie, L., Xu, L., Mullenders, J., Ntziachristos, P., ... Aifantis, I. (2013). The ubiquitin ligase FBXW7 modulates leukemia-initiating cell activity by regulating MYC stability. *Cell 153*(7), 1552–1566. https://doi.org/10.1016/j.cell.2013.05.041.

Knoechel, B., Roderick, J. E., Williamson, K. E., Zhu, J., Lohr, J. G., Cotton, M. J., ... Bernstein, B. E. (2014). An epigenetic mechanism of resistance to targeted therapy in T cell acute lymphoblastic leukemia. *Nature Genetics 46*, 364. https://doi.org/10.1038/ng.2913https://www.nature.com/articles/ng.2913 (supplementary-information).

Kon, A., Shih, L. Y., Minamino, M., Sanada, M., Shiraishi, Y., Nagata, Y., ... Ogawa, S. (2013). Recurrent mutations in multiple components of the cohesin complex in myeloid neoplasms. *Nature Genetics 45*(10), 1232–1237. https://doi.org/10.1038/ng.2731.

Krijger, P. H., & de Laat, W. (2016). Regulation of disease-associated gene expression in the 3D genome. *Nature Reviews. Molecular Cell Biology 17*(12), 771–782. https://doi.org/10.1038/nrm.2016.138.

Kwiatkowski, N., Zhang, T., Rahl, P. B., Abraham, B. J., Reddy, J., Ficarro, S. B., ... Gray, N. S. (2014). Targeting transcription regulation in cancer with a covalent CDK7 inhibitor. *Nature 511*(7511), 616–620. https://doi.org/10.1038/nature13393.

Lancho, O., & Herranz, D. (2018). The MYC enhancer-ome: Long-range transcriptional regulation of MYC in Cancer. *Trends in Cancer 4*(12), 810–822. https://doi.org/10.1016/j.trecan.2018.10.003.

Lawrence, M. S., Stojanov, P., Mermel, C. H., Robinson, J. T., Garraway, L. A., Golub, T. R., ... Getz, G. (2014). Discovery and saturation analysis of cancer genes across 21 tumour types. *Nature 505*, 495. https://doi.org/10.1038/nature12912https://www.nature.com/articles/nature12912 (supplementary-information).

Levine, M., Cattoglio, C., & Tjian, R. (2014). Looping back to leap forward: Transcription enters a new era. *Cell 157*(1), 13–25. https://doi.org/10.1016/j.cell.2014.02.009.

Lieberman-Aiden, E., Berkum, N. L., Williams, L., Imakaev, M., Ragoczy, T., & Telling, A. (2009). Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science 326*. https://doi.org/10.1126/science.1181369.

Loven, J., Hoke, H. A., Lin, C. Y., Lau, A., Orlando, D. A., Vakoc, C. R., ... Young, R. A. (2013). Selective inhibition of tumor oncogenes by disruption of super-enhancers. *Cell 153*(2), 320–334. https://doi.org/10.1016/j.cell.2013.03.036.

Mack, S. C., Pajtler, K. W., Chavez, L., Okonechnikov, K., Bertrand, K. C., Wang, X., ... Rich, J. N. (2017). Therapeutic targeting of ependymoma as informed by oncogenic enhancer profiling. *Nature 553*, 101. https://doi.org/10.1038/nature25169https://www.nature.com/articles/nature25169 (supplementary-information).

Mansour, M. R., Abraham, B. J., Anders, L., Berezovskaya, A., Gutierrez, A., Durbin, A. D., ... Look, A. T. (2014). Oncogene regulation. An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. *Science 346*(6215), 1373–1377. https://doi.org/10.1126/science.1259037.

Maurano, M. T., Humbert, R., Rynes, E., Thurman, R. E., Haugen, E., Wang, H., ... Stamatoyannopoulos, J. A. (2012). Systematic localization of common disease-associated variation in regulatory DNA. *Science 337*(6099), 1190–1195. https://doi.org/10.1126/science.1222794.

Mazumdar, C., Shen, Y., Xavy, S., Zhao, F., Reinisch, A., Li, R., ... Majeti, R. (2015). Leukemia-associated Cohesin mutants dominantly enforce stem cell programs and impair human hematopoietic progenitor differentiation. *Cell Stem Cell 17*(6), 675–688. https://doi.org/10.1016/j.stem.2015.09.017.

McKeown, M. R., Corces, M. R., Eaton, M. L., Fiore, C., Lee, E., Lopez, J. T., ... Majeti, R. (2017). Superenhancer analysis defines novel Epigenomic subtypes of non-APL AML, including an RARα dependency targetable by SY-1425, a potent and selective RARα agonist. *Cancer Discovery 7*(10), 1136–1153. https://doi.org/10.1158/2159-8290.cd-17-0399.

Mertz, J. A., Conery, A. R., Bryant, B. M., Sandy, P., Balasubramanian, S., Mele, D. A., ... Sims, R. J., III (2011). Targeting MYC dependence in cancer by inhibiting BET bromodomains. *Proceedings of the National Academy of Sciences of the United States of America 108*(40), 16669–16674. https://doi.org/10.1073/pnas.1108190108.

Minzel, W., Venkatachalam, A., Fink, A., Hung, E., Brachya, G., Burstain, I., ... Ben-Neriah, Y. (2018). Small molecules co-targeting CKIα and the transcriptional kinases CDK7/9 control AML in preclinical models. *Cell 175*(1), 171–185 e125 https://doi.org/10.1016/j.cell.2018.07.045.

Molliex, A., Temirov, J., Lee, J., Coughlin, M., Kanagaraj, A. P., Kim, H. J., ... Taylor, J. P. (2015). Phase separation by low complexity domains promotes stress granule assembly and drives pathological fibrillization. *Cell 163*(1), 123–133. https://doi.org/10.1016/j.cell.2015.09.015.

Mullenders, J., Aranda-Orgilles, B., Lhoumaud, P., Keller, M., Pae, J., Wang, K., ... Aifantis, I. (2015). Cohesin loss alters adult hematopoietic stem cell homeostasis, leading to myeloproliferative neoplasms. *The Journal of Experimental Medicine 212*(11), 1833–1850. https://doi.org/10.1084/jem.20151323.

Nicodeme, E., Jeffrey, K. L., Schaefer, U., Beinke, S., Dewell, S., Chung, C. -W., ... Tarakhovsky, A. (2010). Suppression of inflammation by a synthetic histone mimic. *Nature 468*(7327), 1119–1123. https://doi.org/10.1038/nature09589.

Nora, E. P., Goloborodko, A., Valton, A. -L., Gibcus, J. H., Uebersohn, A., Abdennur, N., ... Bruneau, B. G. (2017). Targeted degradation of CTCF decouples local insulation of

chromosome domains from genomic compartmentalization. *Cell 169*(5), 930–944 (e922) https://doi.org/10.1016/j.cell.2017.05.004.
Northcott, P. A., Buchhalter, I., Morrissy, A. S., Hovestadt, V., Weischenfeldt, J., Ehrenberger, T., ... Lichter, P. (2017). The whole-genome landscape of medulloblastoma subtypes. *Nature 547*, 311. https://doi.org/10.1038/nature22973https://www.nature.com/articles/nature22973 (supplementary-information).
Northcott, P. A., Lee, C., Zichner, T., Stutz, A. M., Erkek, S., Kawauchi, D., ... Pfister, S. M. (2014). Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. *Nature 511*(7510), 428–434. https://doi.org/10.1038/nature13379.
Oldridge, D. A., Wood, A. C., Weichert-Leahey, N., Crimmins, I., Sussman, R., Winter, C., ... Maris, J. M. (2015). Genetic predisposition to neuroblastoma mediated by a LMO1 super-enhancer polymorphism. *Nature 528*, 418. https://doi.org/10.1038/nature15540https://www.nature.com/articles/nature15540 (supplementary-information).
Ooi, W. F., Xing, M., Xu, C., Yao, X., Ramlee, M. K., Lim, M. C., ... Tan, P. (2016). Epigenomic profiling of primary gastric adenocarcinoma reveals super-enhancer heterogeneity. *Nature Communications 7*, 12983. https://doi.org/10.1038/ncomms12983https://www.nature.com/articles/ncomms12983 (supplementary-information).
Pomerantz, M. M., Ahmadiyeh, N., Jia, L., Herman, P., Verzi, M. P., Doddapaneni, H., ... Freedman, M. L. (2009). The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. *Nature Genetics 41*(8), 882–884. https://doi.org/10.1038/ng.403.
Puissant, A., Frumm, S. M., Alexe, G., Bassil, C. F., Qi, J., Chanthery, Y. H., ... Stegmaier, K. (2013). Targeting MYCN in neuroblastoma by BET bromodomain inhibition. *Cancer Discovery 3*(3), 308–323. https://doi.org/10.1158/2159-8290.CD-12-0418.
Rao, S. S. P., Huang, S. -C., Glenn St Hilaire, B., Engreitz, J. M., Perez, E. M., Kieffer-Kwon, K. -R., ... Aiden, E. L. (2014). Cohesin loss eliminates all loop domains. *Cell 171*(2), 305–320 (e324) https://doi.org/10.1016/j.cell.2017.09.026.
Rao, S. S. P., Huntley, M. H., Durand, N. C., Stamenova, E. K., Bochkov, I. D., & Robinson, J. T. (2014). A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. *Cell 159*. https://doi.org/10.1016/j.cell.2014.11.021.
Rathert, P., Roth, M., Neumann, T., Muerdter, F., Roe, J. -S., Muhar, M., ... Zuber, J. (2015). Transcriptional plasticity promotes primary and acquired resistance to BET inhibition. *Nature 525*, 543. https://doi.org/10.1038/nature14898https://www.nature.com/articles/nature14898 (supplementary-information).
Roadmap Epigenomics, C., Kundaje, A., Meuleman, W., Ernst, J., Bilenky, M., Yen, A., ... Kellis, M. (2015). Integrative analysis of 111 reference human epigenomes. *Nature 518*, 317. https://doi.org/10.1038/nature14248https://www.nature.com/articles/nature14248 (supplementary-information).
Roe, J. -S., Hwang, C. -I., Somerville, T. D. D., Milazzo, J. P., Lee, E. J., Da Silva, B., ... Vakoc, C. R. (2017). Enhancer reprogramming promotes pancreatic cancer metastasis. *Cell 170*(5), 875–888 (e820) https://doi.org/10.1016/j.cell.2017.07.007.
Ryan, R. J. H., Petrovic, J., Rausch, D. M., Zhou, Y., Lareau, C. A., Kluk, M. J., ... Pear, W. S. (2017). A B cell Regulome links Notch to downstream oncogenic pathways in small B cell lymphomas. *Cell Reports 21*(3), 784–797. https://doi.org/10.1016/j.celrep.2017.09.066.
Sabari, B. R., Dall'Agnese, A., Boija, A., Klein, I. A., Coffey, E. L., Shrinivas, K., ... Young, R. A. (2018). Coactivator condensation at super-enhancers links phase separation and gene control. *Science 361*(6400). https://doi.org/10.1126/science.aar3958.
Sanborn, A. L., Rao, S. S., Huang, S. C., Durand, N. C., Huntley, M. H., Jewett, A. I., ... Aiden, E. L. (2015). Chromatin extrusion explains key features of loop and domain formation in wild-type and engineered genomes. *Proceedings of the National Academy of Sciences of the United States of America 112*(47), E6456–E6465. https://doi.org/10.1073/pnas.1518552112.
Schaub, M. A., Boyle, A. P., Kundaje, A., Batzoglou, S., & Snyder, M. (2012). Linking disease associations with regulatory information in the human genome. *Genome Research 22*(9), 1748–1759. https://doi.org/10.1101/gr.136127.111.
Sengupta, S., & George, R. E. (2017). Super-enhancer-driven transcriptional dependencies in cancer. *Trends Cancer 3*(4), 269–281. https://doi.org/10.1016/j.trecan.2017.03.006.
Sexton, T., & Cavalli, G. (2015). The role of chromosome domains in shaping the functional genome. *Cell 160*(6), 1049–1059. https://doi.org/10.1016/j.cell.2015.02.040.
Sexton, T., Yaffe, E., Kenigsberg, E., Bantignies, F., Leblanc, B., & Hoichman, M. (2012). Three-dimensional folding and functional organization principles of the drosophila genome. *Cell 148*. https://doi.org/10.1016/j.cell.2012.01.010.
Shi, J., Whyte, W. A., Zepeda-Mendoza, C. J., Milazzo, J. P., Shen, C., Roe, J. -S., ... Vakoc, C. R. (2013). Role of SWI/SNF in acute leukemia maintenance and enhancer-mediated Myc regulation. *Genes & Development 27*(24), 2648–2662. https://doi.org/10.1101/gad.232710.113.
Shin, H. Y., Willi, M., HyunYoo, K., Zeng, X., Wang, C., Metser, G., & Hennighausen, L. (2016). Hierarchy within the mammary STAT5-driven Wap super-enhancer. *Nature Genetics 48*(8), 904–911. https://doi.org/10.1038/ng.3606.
Shin, Y., & Brangwynne, C. P. (2017). Liquid phase condensation in cell physiology and disease. *Science 357*(6357). https://doi.org/10.1126/science.aaf4382.
Shu, S., Lin, C. Y., He, H. H., Witwicki, R. M., Tabassum, D. P., Roberts, J. M., ... Polyak, K. (2016). Response and resistance to BET bromodomain inhibitors in triple-negative breast cancer. *Nature 529*, 413. https://doi.org/10.1038/nature16508https://www.nature.com/articles/nature16508 (supplementary-information).
Sotelo, J., Esposito, D., Duhagon, M. A., Banfield, K., Mehalko, J., Liao, H., ... Wu, X. (2010). Long-range enhancers on 8q24 regulate c-Myc. *Proceedings of the National Academy of Sciences of the United States of America 107*(7), 3001–3005. https://doi.org/10.1073/pnas.0906067107.
Spielmann, M., Lupianez, D. G., & Mundlos, S. (2018). Structural variation in the 3D genome. *Nature Reviews. Genetics*. https://doi.org/10.1038/s41576-018-0007-0.
Spitz, F., & Furlong, E. E. (2012). Transcription factors: From enhancer binding to developmental control. *Nature Reviews. Genetics 13*(9), 613–626. https://doi.org/10.1038/nrg3207.
Stratikopoulos, E. E., Dendy, M., Szabolcs, M., Khaykin, A. J., Lefebvre, C., Zhou, M. M., & Parsons, R. (2015). Kinase and BET inhibitors together clamp inhibition of PI3K signaling and overcome resistance to therapy. *Cancer Cell 27*(6), 837–851. https://doi.org/10.1016/j.ccell.2015.05.006.
Sur, I., & Taipale, J. (2016). The role of enhancers in cancer. *Nature Reviews Cancer 16*, 483. https://doi.org/10.1038/nrc.2016.62.
Sur, I. K., Hallikas, O., Vähärautio, A., Yan, J., Turunen, M., Enge, M., ... Taipale, J. (2012). Mice lacking a Myc enhancer that includes human SNP rs6983267 are resistant to intestinal tumors. *Science 338*(6112), 1360–1363. https://doi.org/10.1126/science.1228606.
Taub, R., Kirsch, I., Morton, C., Lenoir, G., Swan, D., Tronick, S., ... Leder, P. (1982). Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. *Proceedings of the National Academy of Sciences of the United States of America 79*(24), 7837–7841.
Taylor, C. F., Platt, F. M., Hurst, C. D., Thygesen, H. H., & Knowles, M. A. (2014). Frequent inactivating mutations of STAG2 in bladder cancer are associated with low tumour grade and stage and inversely related to chromosomal copy number changes. *Human Molecular Genetics 23*(8), 1964–1974. https://doi.org/10.1093/hmg/ddt589.
Turcan, S., Rohle, D., Goenka, A., Walsh, L. A., Fang, F., Yilmaz, E., ... Chan, T. A. (2012). IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature 483*(7390), 479–483. https://doi.org/10.1038/nature10866.
Tuupanen, S., Turunen, M., Lehtonen, R., Hallikas, O., Vanharanta, S., Kivioja, T., ... Aaltonen, L. A. (2009). The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling. *Nature Genetics 41*, 885. https://doi.org/10.1038/ng.406https://www.nature.com/articles/ng.406 (supplementary-information).
Vian, L., Pekowska, A., Rao, S. S. P., Kieffer-Kwon, K. R., Jung, S., Baranello, L., ... Casellas, R. (2018). The energetics and physiological impact of Cohesin extrusion. *Cell 173*(5), 1165–1178 e1120 https://doi.org/10.1016/j.cell.2018.03.072.
Viny, A. D., Ott, C. J., Spitzer, B., Rivas, M., Meydan, C., Papalexi, E., ... Levine, R. L. (2015). Dose-dependent role of the cohesin complex in normal and malignant hematopoiesis. *The Journal of Experimental Medicine 212*(11), 1819–1832. https://doi.org/10.1084/jem.20151317.
Wang, H., Maurano, M. T., Qu, H., Varley, K. E., Gertz, J., Pauli, F., ... Stamatoyannopoulos, J. A. (2012). Widespread plasticity in CTCF occupancy linked to DNA methylation. *Genome Research 22*(9), 1680–1688. https://doi.org/10.1101/gr.136101.111.
Wang, Y., Zhang, T., Kwiatkowski, N., Abraham, B. J., Lee, T. I., Xie, S., ... Zhao, J. J. (2015). CDK7-dependent transcriptional addiction in triple-negative breast cancer. *Cell 163*(1), 174–186. https://doi.org/10.1016/j.cell.2015.08.063.
Wasserman, N. F., Aneas, I., & Nobrega, M. A. (2010). An 8q24 gene desert variant associated with prostate cancer risk confers differential in vivo activity to a MYC enhancer. *Genome Research 20*(9), 1191–1197. https://doi.org/10.1101/gr.105361.110.
Weintraub, A. S., Li, C. H., Zamudio, A. V., Sigova, A. A., Hannett, N. M., Day, D. S., ... Young, R. A. (2017). YY1 is a structural regulator of enhancer-promoter loops. *Cell 171*(7), 1573–1588 e1528 https://doi.org/10.1016/j.cell.2017.11.008.
Weischenfeldt, J., Dubash, T., Drainas, A. P., Mardin, B. R., Chen, Y., Stutz, A. M., ... Korbel, J. O. (2017). Pan-cancer analysis of somatic copy-number alterations implicates IRS4 and IGF2 in enhancer hijacking. *Nature Genetics 49*(1), 65–74. https://doi.org/10.1038/ng.3722.
Whyte, W. A., Orlando, D. A., Hnisz, D., Abraham, B. J., Lin, C. Y., Kagey, M. H., ... Young, R. A. (2013). Master transcription factors and mediator establish super-enhancers at key cell identity genes. *Cell 153*(2), 307–319. https://doi.org/10.1016/j.cell.2013.03.035.
de Wit, E., Vos, E. S., Holwerda, S. J., Valdes-Quezada, C., Verstegen, M. J., Teunissen, H., ... de Laat, W. (2015). CTCF binding polarity determines chromatin looping. *Molecular Cell 60*(4), 676–684. https://doi.org/10.1016/j.molcel.2015.09.023.
Xu, W., Yang, H., Liu, Y., Yang, Y., Wang, P., Kim, S. H., ... Xiong, Y. (2011). Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. *Cancer Cell 19*(1), 17–30. https://doi.org/10.1016/j.ccr.2010.12.014.
Yamazaki, H., Suzuki, M., Otsuki, A., Shimizu, R., Bresnick, E. H., Engel, J. D., & Yamamoto, M. (2014). A remote GATA2 hematopoietic enhancer drives leukemogenesis in inv(3)(q21;q26) by activating EVI1 expression. *Cancer Cell 25*(4), 415–427. https://doi.org/10.1016/j.ccr.2014.02.008.
Yan, J., Enge, M., Whitington, T., Dave, K., Liu, J., Sur, I., ... Taipale, J. (2013). Transcription factor binding in human cells occurs in dense clusters formed around Cohesin anchor sites. *Cell 154*(4), 801–813. https://doi.org/10.1016/j.cell.2013.07.034.
Yashiro-Ohtani, Y., Wang, H., Zang, C., Arnett, K. L., Bailis, W., Ho, Y., ... Pear, W. S. (2014). Long-range enhancer activity determines Myc sensitivity to Notch inhibitors in T cell leukemia. *Proceedings of the National Academy of Sciences of the United States of America 111*(46), E4946–E4953. https://doi.org/10.1073/pnas.1407079111.
Zanconato, F., Battilana, G., Forcato, M., Filippi, L., Azzolin, L., Manfrin, A., ... Piccolo, S. (2018). Transcriptional addiction in cancer cells is mediated by YAP/TAZ through BRD4. *Nature Medicine 24*(10), 1599–1610. https://doi.org/10.1038/s41591-018-0158-8.
Zhang, X., Choi, P. S., Francis, J. M., Imielinski, M., Watanabe, H., Cherniack, A. D., & Meyerson, M. (2016). Identification of focally amplified lineage-specific super-enhancers in human epithelial cancers. *Nature Genetics 48*(2), 176–182. https://doi.org/10.1038/ng.3470.
Zhou, Q., Li, T., & Price, D. H. (2012). RNA polymerase II elongation control. *Annual Review of Biochemistry 81*, 119–143. https://doi.org/10.1146/annurev-biochem-052610-095910.
Zuber, J., Shi, J., Wang, E., Rappaport, A. R., Herrmann, H., Sison, E. A., ... Vakoc, C. R. (2011). RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. *Nature 478*(7370), 524–528. https://doi.org/10.1038/nature10334.
Zuin, J., Dixon, J. R., van der Reijden, M. I. J. A., Ye, Z., Kolovos, P., Brouwer, R. W. W., ... Wendt, K. S. (2014). Cohesin and CTCF differentially affect chromatin architecture and gene expression in human cells. *Proceedings of the National Academy of Sciences 111*(3), 996–1001. https://doi.org/10.1073/pnas.1317788111.