Enhancer function regulated by combinations of transcription factors and cofactors

Takeya Nakagawa  |  Mitsuhiro Yoneda  |  Miki Higashi  |  Yoshiaki Ohkuma  |  Takashi Ito

Abstract
Regulation of the expression of diverse genes is essential for making possible the complexity of higher organisms, and the temporal and spatial regulation of gene expression allows for the alteration of cell types and growth patterns. A critical component of this regulation is the DNA sequence-specific binding of transcription factors (TFs). However, most TFs do not independently participate in gene transcriptional regulation, because they lack an effector function. Instead, TFs are thought to work by recruiting cofactors, including Mediator complex (Mediator), chromatin-remodeling complexes (CRCs), and histone-modifying complexes (HMCs). Mediator associates with the majority of transcribed genes and acts as an integrator of multiple signals. On the other hand, CRCs and HMCs are selectively recruited by TFs. Although all the pairings between TFs and CRCs or HMCs are not fully known, there are a growing number of established TF–CRC and TF–HMC combinations. In this review, we focused on the most important of these pairings and discuss how they control gene expression.

KEYWORDS
gene expression, transcription, transcription factor, chromatin-remodeling, histone modification

1 | INTRODUCTION
Transcription factors (TFs) regulate gene expression by directly binding to target regulatory regions. Although each TF has a specific recognition sequence, the spectrum of TFs that are expressed in a given cell is variable and depends on temporal and spatial conditions. These variations in the spectrum of TFs present generate different target gene expression profiles in different cells, can induce alterations in cell type, and enable developmental patterning (Lee & Young, 2013). Most TFs lack the effector activity necessary to induce gene expression and therefore cooperate with a cofactor that has such activity (Lambert et al., 2018). The current model of transcription initiation involves a three-step process (Malik & Roeder, 2010). In the first step, TFs bind to their specific binding site in the regulatory region of a target gene. In the second step, TFs recruit a chromatin-remodeling complex (CRC), which mobilizes the nucleosome, and a histone-modifying complex (HMC), which covalently modifies nucleosomal histone tails. In the third step, the Mediator complex (Mediator) is recruited to the enhancer region by TFs. Mediator bridges between TFs and the Pol II
machinery and promotes the formation of the preinitiation complex (PIC). During this process, three types of multiprotein complexes, CRCs, HMCs, and Mediator, play a central role in gene regulation. Mediator is believed to associate with the majority of transcribed genes (Malik & Roeder, 2010). Because multiple pathways responsible for cell growth and differentiation converge on one or more subunits of Mediator through TFs, Mediator is considered to be an integrative hub for transcription regulation (Malik & Roeder, 2010). Mediator regulates gene expression by integrating several TF signals. On the other hand, CRCs and HMCs are selectively recruited by TFs in a context-dependent manner (Reiter, Wienerroither, & Stark, 2017). TFs can exchange their binding partner, which may have the opposite activity as the original binding partner, depending on the temporal and spatial conditions. This means that TFs enable dynamic control of transcriptional on/off switching according to the activity of their binding partner. This property leads to the establishment of context-dependent gene expression profiles. CRCs and HMCs consist of several subunits, including ATP-dependent DNA helicase, histone modification enzymes, and additional factors that have unique activities, such as DNA-binding and protein–protein interactions, and the composition of these complexes is variable, depending on the situation (Ho & Crabtree, 2010; Liang & Crabtree, 2009; Lickert et al., 2004; Wu et al., 2007). Differences in complex composition uniquely specify the binding partners of the complex (Schuettenruber, Bourbon, Croce, & Cavalli, 2017; Wu, 2012). Therefore, the combinatorial functions of TFs with CRCs or HMCs are thought to play critical roles in gene expression control. In this review, to gain insight into the mechanism of context-dependent gene expression control, we focused on well-characterized, specific associations between TFs and CRCs or HMCs.

## 2 | CHROMATIN-REMOULDING COMPLEXES (CRCS)

### 2.1 | ISWI complex

CRCs can be classified into four groups, including the ISWI, SWI/SNF, CHD, and INO80 families, according to their ATPase subunits. ACF is an ISWI heterodimer partner and forms an ISWI family CRC consisting of ACF1 and ISWI (Ito et al., 1999). ACF plays a key role in regulating nucleosome positioning and transcriptional regulation (Ito, Bulger, Pazin, Kobayashi, & Kadonaga, 1997; Ito, Ikehara, Nakagawa, Kraus, & Muramatsu, 2000). In cooperation with the histone chaperone NAP-1, ACF can reconstitute chromatin in vitro (Ito, Bulger, Kobayashi, & Kadonaga, 1996; Nakagawa, Bulger, Muramatsu, & Ito, 2001). The ISWI family has another multisubunit type CRC called the NURF complex that helps activate transcription in vivo by sliding nucleosomes near promoters to make transcriptional factor binding sites accessible (Badenhorst, Voas, Rebay, & Wu, 2002; Tsukiyama & Wu, 1995; Tsukiyama, Daniel, Tamkun, & Wu, 1995; Varga-Weisz et al., 1997).

#### 2.1.1 | Transcription factors that specifically associate with the ISWI complex

TFs such as C/EBPβ and GATA1 are well characterized and known to associate with the ISWI complex. C/EBPs are members of the leucine zipper transcription factor family, which regulate gene expression to control several cellular processes, such as proliferation, differentiation, inflammation, and energy metabolism (Zahnow, 2009). C/EBPβ interacts with the ACF complex and recruits it to the cyclin D1 promoter (Steinberg et al., 2012). The ACF complex then represses cyclin D1 expression by suppressing C/EBPβ transactivation activity.

GATA1 is a member of the GATA transcription family and is a key regulator of the differentiation of erythroid, megakaryocyte, mast, eosinophil, basophil, and dendritic cells (Nei et al., 2013; Vyaz, Ault, Jackson, Orkin, & Shivdasani, 1999; Yu et al., 2002). GATA1 also interacts with ACF (Rodriguez et al., 2005).

### 2.2 | BAF (BRG1/BRM-associated factor) complex

The BAF complex is a SWI/SNF family CRC and a crucial factor regulating gene expression by controlling chromatin dynamics. It is also known that the BAF complex facilitates the reprogramming of somatic cells (Singhal et al., 2010). It consists of two switchable ATPase subunits, either BRM or BRG1, three core subunits (BAF47, BAF155, and BAF170), and at least 15 lineage-specific variant subunits (Phelan, Sif, Narlikar, & Kingston, 1999). These subunit variations enable the assembly of hundreds of distinct combinatorial complexes, generating the capacity to regulate gene expression in a cell lineage-specific pattern (Wang et al., 1996). For example, neuron-specific BAF53b and BAF45b define the neuron-specific nBAF complex (Wu et al., 2007). The ES cell-specific eSBAF complex contains BRG1 and BAF155 but does not include BRM and BAF170 (Ho et al., 2009). The cardiac-specific cBAF complex contains BAF60c and BAF45c (Liang & Crabtree, 2009). PBAF is another analog of the BAF complex that contains BRG1, but not BRM, as well as BAF180 (also known as polybromo 1) and BAF200 (also known as ARID2), but not BAF250 (Yan et al., 2005). The different subunit combinations create unique and complex surfaces that enable diverse interactions with transcription factors. It is, in fact, well established that the BAF complex...
interacts with various TFs and plays diverse roles during mammalian development.

2.2.1 | Transcription factors that specifically associate with the BAF complex

TFs such as MyoD, TBX5, and GATA1 are well characterized and known to associate with the BAF complex. MyoD is a master regulator of skeletal muscle differentiation, is a basic helix–loop–helix (bHLH) type of TF, and forms a heterodimer with the E2A protein. Heterodimeric MyoD binds to E-Box elements and induces gene activation in muscle (Sartorelli & Caretti, 2005; Tapscott, 2005). It also interacts with BAF60c, a variant of BAF60 that is expressed abundantly in skeletal muscle (Wang et al., 1996). BAF60c facilitates MyoD binding to target genes and promotes recruitment of BAF core components (Forcales et al., 2012). The recruited BAF complex remodels chromatin structure and activates MyoD target genes.

TBX5 is a key regulator of cardiac and forelimb development and is a member of the T-box family of transcription factors that share a common T-box DNA-binding domain (Steimle & Moskowitz, 2017). TBX5 interacts with BAF60c, a critical regulator of cardiac myogenesis, and recruits the BAF complex to heart-specific enhancers (Lickert et al., 2010). Pax6 interacts with and acts together with the BAF complex to neurogenic progenitors. The Pax6–BAF complex drives neurogenesis by directly activating other TFs, which is essential for establishing the neurogenic network (Ninkovic et al., 2013).

GATA1 also interacts with the BAF complex and recruits it to the β-globin locus control region. BRG1 then mediates GATA1-dependent chromatin looping and transcriptional activation (Bultman, Gebuhr, & Magnuson, 2005; Kim, Bultman, Kiefer, Dean, & Bresnick, 2009).

The Pax gene family encodes tissue-specific transcription factors and is a key factor in regulating organogenesis and maintaining pluripotency of stem cell populations during the development (Chi & Epstein, 2002). Pax6 is a key regulator of eye development and neurogenesis and is also important in the development of the nose, pancreas, pituitary, and pineal gland (Elvenes, Sjøttem, Holm, Bjorkoy, & Johansen, 2010). Pax6 interacts with and acts together with the BAF complex in neurogenic progenitors. The Pax6–BAF complex drives neurogenesis by directly activating other TFs, which is essential for establishing the neurogenic network (Ninkovic et al., 2013).

Yin Yang 1 (YY1) is well characterized and associates with the INO80 complex. YY1 is a member of the GLI–Krüppel class of proteins, which is ubiquitously expressed and evolutionarily conserved (Thomas & Seto, 1999). YY1 is a multifunctional TF that can either activate or repress transcription by recruiting different cofactor complexes, such as PRC, HAT, or HDAC (Brown, Mucci, Whiteley, Dirksen, & Kassis, 1998; Han et al., 2006; Yao, Yang, & Seto, 2001), and interacts with the INO80 CRC (Jin et al., 2005). BRCA2- and CDKN1A-interacting protein (BCCIP) is an important cofactor for BRCA2 in tumor suppression and a novel target protein component of the INO80–YY1 complex. Both INO80 and YY1 are required to recruit the INO80–YY1 complex to AP-1 is a dimeric transcription factor composed of Jun, Fos, and ATF subunits. AP-1 regulates gene transcription in response to the stimulation of cytokines, growth factors, stress, and bacterial and viral infections (Karin, Liu, & Zandi, 1997). AP-1(FOS/JUN) selects cell lineage-specific enhancers according to extracellular signals and, together with lineage-specific TFs, binds nucleosome-occupied enhancers, recruits the BAF complex, and establishes the accessible chromatin state (Vierbuchen et al., 2017).

GATA3 is a member of the GATA transcription family and interacts with BRG1. GATA3 functions as a “pioneer” factor in the cellular reprogramming event during the mesenchymal-to-epithelial transition (Takaku et al., 2016). GATA3-dependent cellular reprogramming requires recruitment of BRG1 in the context of the mesenchymal-to-epithelial transition.

2.3 | INO80 complex

The INO80 CRC consists of 15 subunits (Shen, Mizuguchi, Hamiche, & Wu, 2000), and it regulates gene expression as well as DNA repair and replication by nucleosome sliding; that is, by exchanging histone H2A.Z with H2A and altering the nucleosome position at the promoter region (Brahma et al., 2017; Papamichos-Chronakis, Watanabe, Rando, & Peterson, 2011; Udagama, Sabri, & Bartholomew, 2011). INO80 itself is an ATP-dependent DNA helicase. Tip49a and Tip49b (yeast Rvb1 and 2) are highly conserved from yeast to human and belong to the AAA+ (an ATPase associated with diverse cellular activity) family of ATPases. Tip49a and Tip49b are essential for the chromatin-remodeling activity of the INO80 complex (Jonsson, Jha, Wohlschlegel, & Dutta, 2004). Arp4, Arp5, and Arp8 are actin-related proteins, whereas Arp5 and Arp8 are also important for the chromatin-remodeling activity of the INO80 complex (Shen, Ranallo, Choi, & Wu, 2003).

2.3.1 | Transcription factors that specifically associate with the INO80 complex

NF-κB has been characterized as a primary Mediator of the immune response. Recently, it has been recognized as a key regulator of physiological contexts such as limb formation and neuronal viability (Bushid et al., 1998; Mattson, Culmsee, Yu, & Camandola, 2000). NF-κB is a promyelinating TF in Schwann cells (Nickols, Valentine, Kanwal, & Carter, 2003), in which it interacts with the BAF complex in response to axonal signaling. During myelination, the BAF complex is activated by the formation of a complex with NF-κB and recruited to the target gene promoter that induces myelination (Limpert et al., 2013).
the BCCIP promoter and thereby facilitate transcription (Su et al., 2016).

3 | HISTONE-MODIFYING COMPLEXES

3.1 | Polycomb repressive complex

Polycomb group (PcG) proteins, which are a set of TFs that specify cell identity along the head-to-tail axis, were initially identified in *Drosophila melanogaster* as negative regulators of homeotic genes (Lewis, 1978). More recently, they have become known as crucial factors maintaining cellular identity in higher eukaryotes (Schuettengruber & Cavalli, 2009). At least 16 PcG proteins have been identified, and some of them are organized into multiprotein complexes. There are two main types of complexes, polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2 (PRC2) (Blackledge, Rose, & Klose, 2015). PRC1 can be further divided into canonical (cPRC1) and noncanonical (ncPRC1) complexes. Both types of PRC1 complex contain two core subunits, RING1A/B and one of six PcG ring finger proteins (PCGF1–6) (Schuettengruber et al., 2017). RING1A/B has E3 ubiquitin ligase activity at histone H2A on lysine 119. PCGFs are required for the enzymatic activity of the complex and define the interaction with additional components to regulate target specificity (Blackledge et al., 2015).

The composition of accessory factors differs between canonical and noncanonical PRC1. Accessory factors modulate their chromatin-binding sites and catalytic activity. cPRC1 contains one chromobox protein (CBX2,4,6–8), which binds H3K27me3 with various affinities, and one polyhomeotic (PH) homolog protein (HPHC1–3), which has a sterile alpha motif (SAM) domain essential for PcG-mediated repression. ncPRC1 contains additional proteins, such as RYBP, KDM2A, DCAF7, and WDR5. Additional components specific to each complex modulate their DNA-binding affinity or enzymatic activity.

Mammalian PRC2 core components consist of enhancer of zet homolog (EZH1/2), suppressor of zet (SUZ12), embryonic ectoderm development (EED), and RBAP47/7 (Simon & Kingston, 2009). EZH1/2 has methyltransferase activity at histone H3 on lysine 27 and is mutually exclusive and differentially expressed (Margueron et al., 2008). EED binds H3K27me3 and might therefore contribute to the self-propagation of H3K27me3 (Margueron et al., 2009). RBBP4/7 stabilizes the complex (Satrimafitrah et al., 2016), whereas PRC2 contains several auxiliary subunits, including JARID2, AEBP2, PCL1–3, EPOP, and LCOR/LCORL, which can modulate PRC2 catalytic activity (Conway et al., 2018). CBX, a core component of cPRC1, binds specifically to trimethylated histone H3 lysine 27, which means that PRC1 functions downstream of PRC2 (Simon & Kingston, 2009). PRCs have no inherent specific DNA-binding activity in mammals; therefore, additional factors are required to recruit them to a specific chromatin site (Yu et al., 2012).

3.1.1 | Transcription factors that specifically associate with PRC complexes

TFs such as REST, RUNX1, and SALL4 are well characterized and known to associate with PRC complexes. RE1-silencing transcription factor (REST, also known as neuron-restrictive silencing factor, NRSF) is a transcription factor that blocks the expression of neuronal genes in non-neuronal tissues (Schoenherr & Anderson, 1995). REST, which interacts with both PRC1 and PRC2, represses a number of neuronal genes before neuronal differentiation (Dietrich et al., 2012). During differentiation, PRC is displaced from REST binding sites and decreases histone H3 methylation; as a result, neuronal genes are activated (Dietrich et al., 2012).

Runt-related transcription factor 1 (RUNX1, also known as AML1 or CBFA2) forms a heterodimer with CBFB. RUNX1 has been identified as a major regulator of hematopoiesis (Chen, Yokomizo, Zeigler, Dzierzak, & Speck, 2009) and hair follicle stem cell activation (Osorio et al., 2008). It is the most common mutational target in human leukemia (Speck & Gilliland, 2002) and is also mutated in myelodysplastic syndrome (Bejar et al., 2011). RUNX1 directly binds BMI-1 (also known as PCGF4), a variable component of PRC1, and recruits PRC1 to the RUNX1 binding sites in primary murine thymocytes (Yu et al., 2012).

SALL4, ZNF281, and SMAD3 were identified as interacting partners of PRC2 (Oliviero et al., 2016). SALL4 recruits PRC2 to the SOX2 and SOX17 loci in embryonic lineages (Abboud et al., 2015). ZNF281 forms part of a pluripotency network that includes SOX2, OCT4, NANOG, and GCFC1 (Wang et al., 2008). SMAD3 is an intracellular Mediator of the TGFβ pathway, which has been implicated in stem cell pluripotency and differentiation (Kim et al., 2011). SALL4 and ZNF281 interact with PRC2 in pluripotent cells, whereas SMAD3 interacts with PRC2 in differentiating cells (Oliviero et al., 2016).

3.2 | Histone deacetylase (HDAC) complexes

Histone deacetylase (HDAC) complexes are a component of multiprotein complexes and has enzymatic activity to remove acetyl residues from nucleosomal histones. Histone deacetylation induces chromatin condensation and results in gene transcriptional repression (Sterner & Berger, 2000). HDAC enzymes also have influence on cell growth and differentiation (Fischer, Sananbenesi, Mungenast, & Tsai, 2010). Eighteen mammalian HDACs are classified into four subclasses according to their structural
and functional similarities (Gray & Ekstrom, 2001). The histone deacetylase activity of class I, II, and IV HDACs depends on Zn^{2+}, whereas class III HDACs require NAD^{+} for their deacetylase activity (Delcuve, Khan, & Davie, 2012).

Class I HDACs (HDAC 1, 2, 3, and 8) are closely related to yeast RPD3 and are ubiquitously expressed in the nucleus (de Ruijter, Gennip, Caron, Kemp, & Kuilenburg, 2003). HDAC1 and 2 are components of multiprotein complexes such as Sin3, NuRD, and CoREST (Delcuve et al., 2012). The mammalian Sin3 complex consists of SIN3A/B, HDAC1/2, RbAp46, RbAp48, SAP18, and SAP30. SIN3A and SIN3B have sequence similarity and overlapping expression patterns but play distinct and nonoverlapping roles. mSin3A is essential for the early developmental preimplantation stage. On the other hand, mSin3B is essential in the late gestation stage (Hayakawa & Nakayama, 2011). Several other factors are associated with the SIN3 complex, including MeCP2, RBP1, NCoR, and SMRT. SAP30 is considered to be a platform for interactions with other factors (Laherty et al., 1998). The CoREST complex was identified as a corepressor of REST and consists of CoREST, HDAC1/2, p80, Sox-like protein, ZNF217, and LSD1. The CoREST protein has two SANT domains, which have been proposed as histone-binding modules (Yu, Li, Ishizuka, Guenther, & Lazar, 2003). The CoREST complex deacetylates histone tails, resulting in hypoacetylated histones that are recognized by CoREST protein, which facilitates the demethylase activity of LSD1 (Shi et al., 2005). HDAC1 and 2 are also subunits of the Nanog- and Oct4-associated deacetylase complex (NODE) (Liang et al., 2008). HDAC3 is a component of the NCoR and SMRT complexes (Delcuve et al., 2012), which bind to nuclear hormone receptors. Both complexes consist of HDAC3, transduction β-like 1 (TBL1), TBL-related 1 (TBLR1), and G protein pathway repressor 2 (GPS2) (Hayakawa & Nakayama, 2011). NCoR, but not SMRT, associates with zinc finger and BTB domain-containing 33 (ZBTB33). NCoR is essential for neural differentiation and the developmental progression of erythrocytes and thymocytes (Hermanson, Jepsen, & Rosenfeld, 2002; Jepsen et al., 2000, 2007). Knockout studies of class I HDACs reveal the relationship between cell proliferation and survival (Haberland, Montgomery, & Olson, 2009).

Class II HDACs (HDAC 4, 5, 6, 7, 9, and 10) have a domain similar to yeast HAD1 and shuttle between the nucleus and the cytoplasm. Class II HDACs have a tissue-specific expression pattern and function. Class IIa HDACs (HDAC4, 5, 7, and 9) associate with NCoR and SMRT complexes (Fischle et al., 2002). The class IV HDAC, HDAC11, is similar to class I and II HDACs, but little is known about its function. Class III HDACs are referred to as sirtuins (SIRT1–7), which have been implicated in metabolism and aging (Imai, Armstrong, Kaebelstein, & Guarente, 2000). HDACs are often deregulated in disease; therefore, inhibition of their deacetylase activity is a therapeutic goal.

### 3.2.1 Transcription factors that specifically associate with HDAC complexes

TFs such as Mad, Ikaros, and RUNX2 are well characterized and known to associate with HDAC complexes. Mad and Max are members of the basic region-helix-loop-helix-leucine zipper (bHLH-Zip) protein family and form a heterodimer, Mad–Max. Max also forms another type of heterodimer, Myc–Max, which activates genes involved in promoting cell proliferation. On the other hand, Mad–Max represses Myc target genes (Laherty et al., 1997). Mad interacts with the SIN3 complex; hence, Mad–Max recruits the SIN3 complex to Myc target genes and represses cell proliferation (Lüscher & Vervoorts, 2012).

Ikaros is a key regulator of lymphocyte differentiation. In multipotent hematopoietic progenitors, Ikaros assists transcriptional priming that promotes lymphocyte differentiation (Yoshida & Georgopoulos, 2014). Ikaros associates with the SIN3 complex in mature T cells (Koipally, Renold, Kim, & Georgopoulos, 1999) and targets target gene expression that depends on the histone deacetylase activity of the SIN3 complex.

Runt-related transcription factor 2 (RUNX2, also known as AML3 or CBFA1) forms a heterodimer with CBFB and is a key regulator of osteoblast development. Mutation of RUNX2 causes the bone disorder cleidocranial dysplasia, which cases dental defects and reduced or absent clavicles (Mundlos et al., 1997). HDAC3 interacts with the N-terminal region of RUNX2, whereas HDAC6 and 7 interact with the C-terminal region of RUNX2 (Jensen, Schroeder, Bailey, Gopalakrishnan, & Westendorf, 2008; Schroeder, Kahler, Li, & Westendorf, 2004; Westendorf et al., 2002). HDAC4 binds to the runt domain and interferes with DNA binding (Jeon et al., 2006; Vega et al., 2004). RUNX2 recruits HDAC3 to osteoblast gene promoters and represses RUNX2-mediated transcription (Schroeder et al., 2004).

GATA3 also interacts with HDAC4, which it recruits to the ILS promoter region and thereby represses ILS gene expression. Furthermore, GATA3 also recruits p300, also known as histone acetyltransferase (HAT), to the same promoter. Dynamic regulation of the ILS gene is achieved by reversible histone modification catalyzed by HDAC4 and p300 (Han et al., 2006).

REST interacts with the SIN3 complex (Huang, Myers, & Dingledine, 1999) and represses transcription of the GRIA2 (also known as GLUR2) gene and the type II sodium channel (SCN2A) gene by recruiting the SIN3 complex in non-neuronal cells. REST also interacts with the CoREST complex (Ballas et al., 2001) and represses transcription of the SCN2A gene by recruiting the CoREST complex in non-neuronal cells.

E2F family TFs are critical for timely activation of target genes involved in DNA replication and cell cycle control.
These TFs form active DNA-binding heterodimers with DP1 or DP2. E2F activity is controlled by its interaction with the pRB family of proteins. E2F TFs recruit SIN3B complexes and repress target gene transcription (Rayman et al., 2002). It is also known that E2F TFs interact with CBP and thereby regulate target gene expression by switching coactivators and corepressors (Trouche, Cook, & Kouzarides, 1996).

BCL-6 is a TF that contains the Cys2–His2 zinc finger and POZ domains. BCL-6 regulates B-cell lymphocyte cell fate in germinal centers by preventing the terminal differentiation of B lymphocytes into plasma cells. BCL-6 interacts with NCoR and SMRT via the POZ domain (Huynh & Bardwell, 1998).

The p53 tumor suppressor regulates a number of genes through transcriptional activation and repression, and it has a critical role in cell cycle control, DNA damage repair, and apoptosis. p53 interacts with the SIN3A complex and represses target gene transcription (Murphy et al., 1999). Specifically, p53 recruits the SIN3A complex to the MAD1 promoter, which is a mitotic check point protein, and represses its transcription (Chun & Jin, 2003).

3.3 Transcription factors that specifically associate with the HAT complex

Well-characterized TFs such as Myc and E2F associate with the HAT complex. Myc and E2F recruit the STAGA or TIP60 complexes, and the HAT activity of these complexes activates gene transcription (Frank et al., 2003; Liu, Tesfai, Evrard, Dent, & Martinez, 2003; Taubert et al., 2004). This recruitment is due to the interaction between TRRAP and Myc or E2F (McMahon et al., 1998). TRRAP interacts with other factors, including p53, E1A, Erα, Erβ, VDR, PPARγ, LXR, FXR, β-catenin, Skp1, and BRCA1. TRRAP may serve as a platform for recruitment of the HAT complex by TFs (Murr, Vaissiere, Sawan, Shukla, & Herceg, 2007). Esa1, a yeast homolog of TIP60, shows a ubiquitous distribution to active promoters. Consistent with this fact, TIP60 has been found to associate with a growing number of TFs (Squatrito, Gorrini, & Amati, 2006).

4 Complexes having both chromatin-remodeling and histone-modifying activities

4.1 Nucleosome remodeling deacetylase (NuRD) complex

The NuRD complex has both chromatin-remodeling and deacetylation activity. NuRD consists of at least eight subunits, including Mi-2, an ATP-dependent helicase (CHD3/4), HDAC1, HDAC2, MTA1/2/3, MBD2/3, RbAp46, and RbAp48 (McDonel, Costello, & Hendrich, 2009). Lysine demethylase 1 (LSD1) is also an integral subunit of the NuRD complex (Wang et al., 2009). CHD3 and CHD4 belong to the chromodomain–helicase–ATP–DNA-binding (CHD) protein family, which is conserved from yeast to human. CHD3 and CHD4 have two plant homeodomain (PHD) zinc finger domains, two chromodomains, and an SWI/SNF type ATP-dependent helicase domain. HDAC1/2 and RbAp46/48 are common to the NuRD and Sin3 complexes. MTA is an alternative subunit and contributes to the functional diversity of these complexes (Bowen, Fujita, Kajita, & Wade, 2004). MTA1 and MTA3 are involved in tumor progression (Fujita et al., 2003; Kumar et al., 2002), whereas MBD2 and MBD3 are members of the methyl-CpG-binding domain (MBD) family, although MBD3 is unable to bind methyl-CpG (Saito & Ishikawa, 2002). MBD2 and MBD3 have a high degree of similarity, but only MBD3 is essential for mouse development (Hendrich, Guy, Ramsahoye, Wilson, & Bird, 2001). NuRD is a key regulator of stem cell maintenance and differentiation, cell proliferation, and the epithelial-to-mesenchymal transition (Basta & Rauchman, 2015; Fujita et al., 2003; Yoshida et al., 2008).

4.1.1 Transcription factors that specifically associate with the NuRD complex

TFs such as Ikaros, SALL1, and SALL4 are well-characterized and known to associate with the NuRD complex. Ikaros associates with this complex in lymphocytes and erythrocytes (Kim et al., 1999; Sridharan & Smale, 2007).
Ikaros and NuRD cooperatively regulate lymphoid-specific genes to control lymphocyte development and prevent leukemogenesis (Zhang et al., 2011).

SALL1 is a member of the spalt-like gene family and is involved in kidney organogenesis (Osafune, Takasato, Kispert, Asashima, & Nishinakamura, 2006). Mutation of SALL1 leads to Townes–Brocks syndrome, an autosomal-dominant disorder associated with multiorgan defects, such as renal hypoplasia, cystic kidneys, and renal agenesis (Kohlhase, Wischermann, Reichenbach, Froster, & Engel, 1998). SALL1 is known as a transcriptional repressor by its localization in heterochromatin and recruitment of the NuRD complex (Kiefer, McDill, Yang, & Rauchman, 2002), which is required in renal progenitor cells during embryonic kidney development. (Denner & Rauchman, 2013).

SALL4 is also a member of the spalt-like gene family and is essential for early mammalian development. Mutations of SALL4 lead to Okihiro syndrome (Kohlhase et al., 2005), and it is known that SALL4 plays an important role in maintaining the pluripotent properties of embryonic stem cells by regulating key pluripotency genes (Miller et al., 2016). SALL4 represses the expression of target genes, PTEN and SALL1, by recruiting the NuRD complex (Lu et al., 2009).

BCL-6 also interacts with the NuRD complex, and this interaction is critical for the B lymphocyte-specific transcriptional pattern (Fujita et al., 2004).

Nanog and OCT4 are critical TFs for the self-renewal and pluripotency of ES cells, and they form a unique, NuRD-like repressor complex known as Nanog and OCT4-associated deacetylase (NODE) (Liang et al., 2008).

## 5 | DISCUSSION

To date, we have found few functional combinations involving TFs and CRCs or HMCs, but the search for such interactions is just beginning. The majority of those discovered so far play an important role in cell fate determination, making it worthwhile to seek additional candidate interactions. We listed complexes engaging in the development of blood, muscle, nervous tissue, and bone as well as pluripotency maintenance, the immune response, and tumor suppression (Table 1). In each case, key regulatory factors for each cell lineage recruit CRCs or HMCs to their target genes. Some TFs that are enumerated in this review, including OCT4, GATA1, GATA3, p53, and NF-xB, are categorized as “pioneer” transcription factors (Iwafuchi-Doi & Zaret, 2014; Mayran & Drouin, 2018; Qiao et al., 2016; Sammons, Zhu, Drake, & Berger, 2015). Pioneer factors play crucial roles in initiating cell programming and reprogramming, and they have the ability to recognize their target sequences in compacted or closed chromatin and then locally open the chromatin structure.

### Table 1: Overview of interaction between TFs and cofactors

| Cofactor Transcription factors | Cell type                  |
|-------------------------------|-----------------------------|
| Chromatin-remodeling complex  |                             |
| ACF complex C/EBP             | (cell proliferation)        |
| ACF complex GATA1             | Blood                      |
| BAF complex MyoD              | Skeletal muscle            |
| BAF complex TBX5              | Heart                      |
| BAF complex GATA1             | Blood                      |
| BAF complex Pax6              | Neuron                     |
| BAF complex NF-B              | Neuron                     |
| BAF complex API               | (enhancer selection)       |
| BAF complex GATA3             | (mesenchymal to epithelial transition) |
| INO80                         | YY1                        |
| SIN3                          | Ikaros                     |
| (HDAC3, 4, 6, 7)              | RUNX2                      |
| (HDAC4)                       | GATA3                      |
| SIN3, CoREST                  | REST                       |
| SIN3B                         | E2F                        |
| N-CoR, SMRT                   | BCL-6                      |
| SIN3A                         | p53                        |
| STAGA, TIP60                  | Myc                        |
| STAGA, TIP60                  | E2F                        |
| Chromatin-remodeling and histone modifying complex | |
| NuRD complex Ikaros           | Blood                      |
| NuRD complex SALL1            | Kidney cell                |
| NuRD complex SALL4            | ES cell                    |
| NuRD complex BCL-6            | Blood                      |
| NODE complex Nanog, OCT4      | ES cell                    |


to provide accessibility to nonpioneer TFs (Iwafuchi-Doi, 2018). The pioneer factor GATA3 interacts with BRG1 and requires the remodeling activity of BRG1 for its pioneer activity (Takaku et al., 2016). At the IL-5 promoter, GATA3 also interacts with HDAC4 and represses gene transcription (Han et al., 2006). In response to a differentiation stimulus, GATA3 and several nonpioneer TFs cooperatively recruit p300 and promote IL-5 expression. We therefore propose a new model of transcriptional regulation by TFs and cofactors (Figure 1). Pioneer factors bind closed chromatin and recruit, if necessary, transcriptionally repressive HMCs to their target genes until cell reprogramming is initiated. Pioneer factors then recruit CRCs, which open the chromatin structure to increase accessibility for nonpioneer TFs. Pioneer factors or other TFs recruit transcriptionally positive HMCs and subsequently recruit Mediator, which integrates the signals from multiple pathways through TFs and promotes PIC formation (Malik & Roeder, 2010).

According to the histone code hypothesis, combinations of histone modifications have functions that are distinct from those of the individual modifications; therefore, multiple histone modifications contribute to more diverse transcriptional regulation (Fischle, Wang, & Allis, 2003; Jenuwein & Allis, 2001; Kouzarides, 2007; Lee, Smith, & Shilatifard, 2010). Two examples are SALL4, which associates with the PRC, which in turn has histone H2A ubiquitylase and histone H3K27 methylase activities, or NuRD complexes, which have histone deacetylase 1 and 2 (HDAC1, HDAC2) activity. REST also associates with the PRC or HDAC complexes. These TFs have the ability to control multiple modifications of histone tails. These examples suggest that TFs establish diverse transcriptional activities by regulating combinatorial patterns of histone modification.
It is widely accepted that nuclear architecture and chromatin dynamics in the nucleus contribute to gene regulation. Nuclear architecture in the mammalian nucleus is compartmentalized based on chromosome territories (CTs) and the interchromatin compartment (IC), which contains the machinery required for replication, transcription, splicing, and repair (Cremer & Cremer, 2001). During erythroid maturation, the β-globin locus forms chromatin loops between the locus control region, and it expands from the CT surface into the IC space (Rogoczy, Bender, Telling, Byron, & Groudine, 2006). The protruded β-globin locus engages with TFs, and it is known that RNA polymerase II is accumulated and that expression of the β-globin gene is strongly activated. BRG1 is recruited to the β-globin locus by GATA1, and it is essential for establishing chromatin loops (Kim et al., 2009). These findings suggest the possibility that associations between TFs and cofactors also play an important role in gene regulation by influencing the spatial positioning of chromatin within the nucleus.

There is evidence that TFs switch partner complexes depending on differentiation stage. On the other hand, CRCs and HMCs alter their binding partners during differentiation. This high degree of flexibility makes it possible to regulate gene expression more dynamically. Regarding the BAF complex, the tissue-specific subunit BAF60c facilitates TF binding to target genes. This example suggests the possibility that TFs and CRCs or HMCs cooperatively increase target specificity. It is noteworthy that some TFs are related to diseases, and the interactions between TFs and CRCs or HMCs could be therapeutic targets. The growing list of multiprotein complexes gives us a more detailed understanding of transcriptional regulation in the development and disease.

CONFLICT OF INTEREST

None to declare.

ORCID

Takashi Ito http://orcid.org/0000-0002-8984-0318

REFERENCES

Ababdou, N., Moore-Morris, T., Hiriart, E., Yang, H., Bezerra, H., Gualazzi, M. G., ... Puceat, M. (2015). A cohesin-OCT4 complex mediates Sox enhancers to prime an early embryonic lineage. Nature Communications, 6, 6749. https://doi.org/10.1038/ncomms7749

Badenhorst, P., Voas, M., Rebey, I., & Wu, C. (2002). Biological functions of the ISWI chromatin remodeling complex NURF. Genes & Development, 16, 3186–3198. https://doi.org/10.1101/gad.1032202

Ballas, N., Battaglioli, E., Atouf, F., Andres, M. E., Chenoweth, J., Anderson, M. E., ... Mandel, G. (2001). Regulation of neuronal traits by a novel transcriptional complex. Neuron, 31, 353–365. https://doi.org/10.1016/S0896-6273(01)00371-3

Basta, J., & Rauchman, M. (2015). The nucleosome remodeling and deacetylase complex in development and disease. Translational Research : the Journal of Laboratory and Clinical Medicine, 165, 36–47. https://doi.org/10.1016/j.trsl.2014.05.003

Bejar, R., Stevenson, K., Abdel-Wahab, O., Galli, N., Nilsson, B., Garcia-Manero, G., ... Ebert, B. L. (2011). Clinical effect of point mutations in myelodysplastic syndromes. The New England Journal of Medicine, 364, 2496–2506. https://doi.org/10.1056/NEJMoa1013343

Blackledge, N. P., Rose, N. R., & Klose, R. J. (2015). Targeting Polycomb systems to regulate gene expression: Modifications to a complex story. Nature Reviews Molecular Cell Biology, 16, 643–649. https://doi.org/10.1038/nrm4067

Bowen, N. J., Fujita, N., Kajita, M., & Wade, P. A. (2004). Mi-2/ NuRD: Multiple complexes for many purposes. Biochimica Et Biophysica Acta, 1677, 52–57. https://doi.org/10.1016/j.bbaexp.2003.10.010

Brahma, S., Udagawa, M. I., Kim, J., Hada, A., Bhaward, S. K., Hailu, S. G., ... Bartholomew, B. (2017). INO80 exchanges H2A.Z for H2A by translocating on DNA proximal to histone dimers. Nature Communications, 8, 15616. https://doi.org/10.1038/ncomms15616

Brown, J. L., Mucci, D., Whiteley, M., Dirksen, M. L., & Kassis, J. A. (1998). The Drosophila polycomb group gene pleiohomeotic encodes a DNA binding protein with homology to the transcription factor YY1. Molecular Cell, 1, 1057–1064. https://doi.org/10.1016/S1097-2765(00)80106-9

Bultman, S. J., Geburz, T. C., & Magnuson, T. (2005). A Brg1 mutation that uncouples ATPase activity from chromatin remodeling reveals an essential role for SWI/SNF-related complexes in beta-globin expression and erythroid development. Genes & Development, 19, 2849–2861.

Bushdid, P. B., Brantley, D. M., Yull, F. E., Blueuer, G. L., Hoffman, L. H., Niswander, L., & Kerr, L. D. (1998). Inhibition of NF-kappaB activity results in disruption of the apical ectodermal ridge and aberrant limb morphogenesis. Nature, 392, 615–618.

Cai, Y., Jin, J., Tomomori-Sato, C., Sato, S., Sorokina, I., Parmely, T. J., ... Conaway, J. W. (2003). Identification of new subunits of the multiprotein mammalian TRRAP/TIP60-containing histone acetyltransferase complex. The Journal of Biological Chemistry, 278, 42733–42736. https://doi.org/10.1074/jbc.C300389200

Chen, M. J., Yokomizo, T., Zeigler, B. M., Dzierzak, E., & Speck, N. A. (2009). Runx1 is required for the endothelial to haematopoietic transition but not thereafter. Nature, 457, 887–891. https://doi.org/10.1038/nature07619

Chi, N., & Epstein, J. A. (2002). Getting your Pax straight: Pax proteins in development and disease. Trends in Genetics : TIG, 18, 41–47. https://doi.org/10.1016/S0168-9525(01)02594-X

Chun, A. C., & Jin, D. Y. (2003). Transcriptional regulation of mitotic checkpoint gene MAD1 by p53. The Journal of Biological Chemistry, 278, 37439–37450.

Conway, E., Jerman, E., Healy, E., Ito, S., Holoch, D., Oliviero, G., ... Bracken, A. P. (2018). A family of vertebrate-specific polycomb complexes encoded by the LCR/LCRL genes balance PRC2 subtype activities. Molecular Cell, 70(408–421), e408. https://doi.org/10.1016/j.molcel.2018.03.005

Cremer, T., & Cremer, C. (2001). Chromosome territories, nuclear architecture and gene regulation in mammalian cells. Nature Reviews Genetics, 2, 292–301.

de Ruijter, A. J., van Gennip, A. H., Caron, H. N., Kemp, S., & van Kuilenburg, A. B. (2003). Histone deacetylases (HDACs):
Characterization of the classical HDAC family. The Biochemical Journal, 370, 737–749. https://doi.org/10.1042/bj20021321
Delucue, G. P., Khan, D. H., & Davie, J. R. (2012). Roles of histone deacetylases in epigenetic regulation: Emerging paradigms from studies with inhibitors. Clinical Epigenetics, 4, S. https://doi.org/10.1186/1868-7083-4-5
Denner, D. R., & Rauchman, M. (2013). Mi-2/NuRD is required in renal progenitor cells during embryonic kidney development. Developmental Biology, 375, 105–116. https://doi.org/10.1016/j.ydbio.2012.11.018
Dietrich, N., Lerdup, M., Landt, E., Agrawal-Singh, S., Bak, M., Tommerup, N., … Hansen, K. (2012). REST-mediated recruitment of polycomb repressor complexes in mammalian cells. PLoS Genetics, 8, e1002494. https://doi.org/10.1371/journal.pgen.1002494
Dyson, N. (1998). The regulation of E2F by pRB-family proteins. Genes & Development, 12, 2245–2262.
Elvenes, J., Sjottem, E., Holm, T., Bjorkoy, G., & Johansen, T. (2010). Pax6 localizes to chromatin-rich territories and displays a slow nuclear mobility altered by disease mutations. Cellular and Molecular Life Sciences : CMLS, 67, 4079–4094. https://doi.org/10.1007/s00018-010-0429-0
Fischer, A., Sananbenesi, F., Mungenast, A., & Tsai, L. H. (2010). Targeting the correct HDAC(s) to treat cognitive disorders. Trends in Pharmacological Sciences, 31, 605–617. https://doi.org/10.1016/j.tips.2010.09.003
Fischle, W., Dequiedt, F., Hendzel, M. J., Guenther, M. G., Lazar, M. A., Voelter, W., & Verdin, E. (2002). Enzymatic activity associated with class II HDACs is dependent on a multiprotein complex containing HDAC3 and SMRT/N-CoR. Molecular Cell, 9, 45–57. https://doi.org/10.1016/S1097-2765(01)00429-4
Fischle, W., Wang, Y., & Allis, C. D. (2003). Histone and chromatin cross-talk. Current Opinion in Cell Biology, 15, 172–183. https://doi.org/10.1016/S0955-0674(03)00013-9
Forcades, S. V., Albini, S., Giordani, L., Malecova, B., Cignolo, L., Chernov, A., … Puri, P. L. (2012). Signal-dependent incorporation of MyoD-BAP60c into Brg1-based SWI/SNF chromatin-remodelling complex. The EMBO Journal, 31, 301–316. https://doi.org/10.1038/emboj.2011.391
Frank, S. R., Parisi, T., Taubert, S., Fernandez, P., Fuchs, M., Chan, H. M., … Amati, B. (2003). MYC recruits the Tip60 histone acetyltransferase complex to chromatin. EMBO Reports, 4, 575–580. https://doi.org/10.1038/sj.embojr.8601861
Fujita, N., Jaye, D. L., Geigerman, C., Akyildiz, A., Mooney, M. R., Boss, J. M., & Wade, P. A. (2004). MTA3 and the Mi-2/NuRD complex regulate cell fate during B lymphocyte differentiation. Cell, 119, 75–86. https://doi.org/10.1016/j.cell.2004.09.014
Fujita, N., Jaye, D. L., Kajita, M., Geigerman, C., Moreno, C. S., & Wade, P. A. (2003). MTA3, a Mi-2/NuRD complex subunit, regulates an invasive growth pathway in breast cancer. Cell, 113, 207–219. https://doi.org/10.1016/S0092-8674(03)00234-4
Gray, S. G., & Ekstrom, T. J. (2001). The human histone deacetylase family. Experimental Cell Research, 262, 75–83. https://doi.org/10.1006/excr.2000.5080
Haberland, M., Montgomerie, R. L., & Olson, E. N. (2009). The many roles of histone deacetylases in development and physiology: Implications for disease and therapy. Nature Reviews Genetics, 10, 32–42. https://doi.org/10.1038/nrg2485
Han, S., Lu, J., Zhang, Y., Cheng, C., Han, L., Wang, X., … Huang, B. (2006). Recruitment of histone deacetylase 4 by transcription factors represses interleukin-5 transcription. The Biochemical Journal, 400, 439–448. https://doi.org/10.1042/BJ20061085
Hayakawa, T., & Nakayama, J. (2011). Physiological roles of class I HDAC complex and histone demethylase. Journal of Biomedicine & Biotechnology, 2011, 129383. https://doi.org/10.1155/2011/129383
Hendrich, B., Gey, J., Ramsahoye, B., Wilson, V. A., & Bird, A. (2001). Closely related proteins MB2D and MB2D3 play distinctive but interacting roles in mouse development. Genes & Development, 15, 710–723. https://doi.org/10.1101/gad.194101
Hermanson, O., Jepsen, K., & Rosenfeld, M. G. (2002). N-CoR controls differentiation of neural stem cells into astrocytes. Nature, 419, 934–939. https://doi.org/10.1038/nature01156
Ho, L., & Crabtree, G. R. (2010). Chromatin remodelling during development. Nature, 463, 474–484. https://doi.org/10.1038/nature08911
Ho, L., Ronan, J. L., Wu, J., Stahl, B. T., Chen, L., Kuo, A., … Crabtree, G. R. (2009). An embryonic stem cell chromatin remodelling complex, eBAC, is essential for embryonic stem cell self-renewal and pluripotency. Proceedings of the National Academy of Sciences of the United States of America, 106, 5181–5186. https://doi.org/10.1073/pnas.0812889106
Huang, Y., Myers, S. J., & Dingleline, R. (1999). Transcriptional repression by REST: Recruitment of Sin3A and histone deacetylase to neuronal genes. Nature Neuroscience, 2, 867–915. https://doi.org/10.1038/13165
Huyhn, K. D., & Bardwell, V. J. (1998). The BCL-6 POZ domain and other POZ domains interact with the co-repressors N-CoR and SMRT. Oncogene, 17, 2473–2484. https://doi.org/10.1038/sj.onc.1202197
Ikura, T., Ogryzko, V. V., Grigoriev, M., Groisman, R., Wang, J., Horikoshi, M., … Nakatani, Y. (2000). Involvement of the Tip60 histone acetylase complex in DNA repair and apoptosis. Cell, 102, 463–473. https://doi.org/10.1016/S0092-8674(00)00051-9
Imai, S., Armstrong, C. M., Kaebelerlein, M., & Guarente, L. (2000). Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature, 403, 795–800. https://doi.org/10.1038/35001622
Ito, T., Bulger, M., Kobayashi, R., & Kodanaga, J. T. (1996). Drosophila NAP-1 is a core histone chaperone that functions in ATP-facilitated assembly of regularly spaced nucleosomal arrays. Molecular and Cellular Biology, 16, 3112–3124. https://doi.org/10.1128/MCB.16.6.3112
Ito, T., Bulger, M., Pazin, M. J., Kobayashi, R., & Kodanaga, J. T. (1997). ACF, an ISWI-containing and ATP-utilizing chromatin assembly and remodeling factor. Cell, 90, 145–155. https://doi.org/10.1016/S0092-8674(00)00321-9
Ito, T., Ikehara, T., Nakagawa, T., Kraus, W. L., & Muramatsu, M. (2000). p300-mediated acetylation facilitates the transfer of histone H2A-H2B dimers from nucleosomes to a histone chaperone. Genes & Development, 14, 1899–1907.
Ito, T., Levenstein, M. E., Pyodorov, D. V., Kutach, A. K., Kobayashi, R., & Kodanaga, J. T. (1999). ACF consists of two subunits, Acf1 and ISWI, that function cooperatively in the ATP-dependent catalysis of chromatin assembly. Genes & Development, 13, 1529–1539. https://doi.org/10.1101/gad.13.12.1529
Iwasfuchi-Doi, M. (2018). The mechanistic basis for chromatin regulation by pioneer transcription factors. Wiley interdisciplinary reviews. Systems Biology and Medicine, e1427. https://doi.org/10.1002/ wsbm.1427
Iwasfuchi-Doi, M., & Zaret, K. S. (2014). Pioneer transcription factors in cell reprogramming. Genes & Development, 28, 2679–2692. https://doi.org/10.1101/gad.253443.114
Jensen, E. D., Schroeder, T. M., Bailey, J., Gopalakrishnan, R., & Westendorf, J. J. (2008). Histone deacetylase 7 associates with Runx2 and represses its activity during osteoblast maturation in a deacetylation-independent manner. *Journal of Bone and Mineral Research, 23*, 361–372. https://doi.org/10.1359/jbmr.071104

Jenuwein, T., & Allis, C. D. (2001). Translating the histone code. *Science, 293*, 1074–1080.

Jeon, E. J., Lee, K. Y., Choi, N. S., Lee, M. H., Kim, H. N., Jin, Y. H., … Bae, S. C. (2006). Bone morphogenetic protein-2 stimulates Runx2 acetylation. *The Journal of Biological Chemistry, 281*, 16502–16511. https://doi.org/10.1074/jbc.M512494200

Jepsen, K., Hermanson, O., Onami, T. M., Gleierhman, A. S., Lunyak, V., McEvilly, R. J., … Rosenfeld, M. G. (2000). Combinatorial roles of the nuclear receptor corepressor in transcription and development. *Cell, 102*, 753–763. https://doi.org/10.1016/S0092-8674(00)00064-7

Jepsen, K., Solum, D., Zhou, T., McEvilly, R. J., Kim, H. J., Glass, C. K., … Rosenfeld, M. G. (2007). SMRT-mediated repression of an H3K27 demethylase in progression from neural stem cell to neuron. *Nature, 450*, 415–419. https://doi.org/10.1038/nature06270

Jin, J., Cai, Y., Yao, T., Gottschalk, A. J., Florens, L., Swanson, S. K., … Karin, M., Liu, Z., & Zandi, E. (1997). AP‐1 function and regulation. *Molecular Cell, 2*, 33–42. https://doi.org/10.1016/S1097-2765(00)80111-2

Laherty, C. D., Billin, A. N., Lavinsky, R. M., Yochum, G. S., Bush, A. C., Sun, J. M., … Eisenman, R. N. (1998). SAP30, a component of the mSin3 coressorplex involved in N-CoR-mediated repression by specific transcription factors. *Molecular Cell, 2*, 33–42. https://doi.org/10.1016/S1097-2765(00)80111-2

Lee, J. S., Smith, E., & Shilatifard, A. (2010). The language of histone cross-talk. *Cell, 142*, 682–685. https://doi.org/10.1016/j.cell.2010.08.011

Lee, T. I., & Young, R. A. (2013). Transcriptional regulation and its misregulation in disease. *Cell, 152*, 1237–1251. https://doi.org/10.1016/j.cell.2013.02.014

Lewis, E. B. (1978). A gene complex controlling segmentation in *Drosophila*. *Science, 276*, 565–570. https://doi.org/10.1126/science.76565a0

Li, G. S., & Crabtree, G. R. (2009). Developmental biology: The early heart remodelled. *Nature, 459*, 654–655. https://doi.org/10.1038/459654a

Li, J., Yan, M., Zhang, Y., Gu, P., Xin, H., Jung, S. Y., … Songyang, Z. (2008). Nanog and Oct4 associate with unique transcriptional repression complexes in embryonic stem cells. *Nature Cell Biology, 10*, 731–739. https://doi.org/10.1038/ncb1736

Lickert, H., Takeuchi, J. K., Von Both, I., Waller, J. R., McAuliffe, F., Adamson, S. L., … Bruneau, B. G. (2004). Baf60c is essential for chromatin remodeling complexes in embryonic stem cells. *Nature Cell Biology, 7*, 654–657. https://doi.org/10.1038/ncb1071

Limpert, A. S., Bai, S., Narayan, M., Wu, J., Yoon, S. O., Carter, B. D., & Lu, Q. R. (2013). NF‐kappaB forms a complex with the chromatin remodeler BRG1 to regulate Schwann cell differentiation. *The Journal of Neuroscience, 33*, 2388–2397.

Liu, X., Tesfai, J., Evrard, Y. A., Dent, S. Y., & Martinez, E. (2003). c-Myc transformation domain recruits the human STAGA complex and requires TRRAP and GCN5 acetylase activity for transcription activation. *The Journal of Biological Chemistry, 278*, 20405–20412. https://doi.org/10.1074/jbc.M211795200

Liu, J., Jeong, H. W., Kong, N., Yang, Y., Carroll, J., Luo, H. R., … Chai, L., (2009). Stem cell factor SALL4 represses the transcriptions of PTEN and SALL1 through an epigenetic repressor complex. *PloS One, 4*, e5577.

Lüscher, B., & Vervoorts, J. (2012). Regulation of gene transcription by the oncoprotein MYC. *Gene, 494*, 145–160. https://doi.org/10.1016/j.gene.2011.12.027

Malik, S., & Roeder, R. G. (2010). The metazoan Mediator co-activator complex as an integrative hub for transcriptional regulation. *Nature Reviews Genetics, 11*, 761–772.

Margueron, R., Justin, N., Ohno, K., Sharpe, M. L., Son, J., Drury, W. J. III, … Gamblin, S. J. (2009). Role of the polycomb protein EED in deacetylase complexes. *The EMBO Journal, 18*, 3090–3100. https://doi.org/10.1038/emboj.18.11.3090

Kouzarides, T. (2007). Chromatin modifications and their function. *Cell, 128*, 693–705. https://doi.org/10.1016/j.cell.2007.02.005

Kumar, R., Wang, R. A., Mazumdar, A., Talukder, A. H., Mandal, M., Yang, Z., … Vadlamudi, R. K. (2002). A naturally occurring MTA1 variant sequesters oestrogen receptor-alpha in the cytoplasm. *Nature, 418*, 654–657.

Kohlhase, J., Wischermann, A., Reichenbach, H., Froster, U., & Engel, W. (1998). Mutations in the SALL1 putative transcription factor gene cause Townes-Brocks syndrome. *Nature Genetics, 18*, 81–83. https://doi.org/10.1038/ng0198-81

Koipally, J., Renold, A., Kim, J., & Georgopoulos, K. (1999). Repression by Ikaros and Aiolos is mediated through histone
the propagation of repressive histone marks. Nature, 461, 762–767. https://doi.org/10.1038/nature08398

Margueron, R., Li, G., Sarma, K., Blais, A., Zavadil, J., Woodcock, C. L., …, Reinberg, D. (2008). EzH1 and EzH2 maintain repressive chromatin through different mechanisms. Molecular Cell, 32, 503–518. https://doi.org/10.1016/j.molcel.2008.11.004

Martinez, E., Kundu, T. K., Fu, J., & Roeder, R. G. (1998). A human SPT3-TAFI13-I-GCN5-L acetylase complex distinct from transcription factor IID. The Journal of Biological Chemistry, 273, 23781–23785.

Mattson, M. P., Culmsee, C., Yu, Z., & Camandola, S. (2000). Roles of nuclear factor kappaB in neuronal survival and plasticity. Journal of Neuroscience, 74, 443–456.

Mayran, A., & Drouin, J. (2018). Pioneer transcription factors shape the epigenetic landscape. The Journal of Biological Chemistry. https://doi.org/10.1074/jbc.R117.001232

McDonel, P., Costello, I., & Hendrich, B. (2009). Keeping things quiet: Roles of NuRD and Sin3 co-repressor complexes during mammalian development. International Journal of Biochemistry & Cell Biology, 41, 108–116. https://doi.org/10.1016/j.biocel.2008.07.022

McMahon, S. B., Van Buskirk, H. A., Dugan, K. A., Copeland, T. D., & Cole, M. D. (1998). The novel ATG-related protein TRRAP is an essential cofactor for the c-Myc and E2F oncoproteins. Cell, 94, 363–374. https://doi.org/10.1016/S0092-8674(00)81479-8

Miller, A., Raiser, M., Kloet, S. L., Loos, R., Nishinakamura, R., Bertone, P., … Hendrich, B. (2016). Sall4 controls differentiation of pluripotent cells independently of the Nucleosome Remodelling and Deacetylation (NuRD) complex. Development, 143, 3074–3084. https://doi.org/10.1242/dev.139113

Mundlos, S., Otto, F., Mundlos, C., Mulliken, J. B., Aylsworth, A. S., Albright, S., … Olsen, B. R. (1997). Mutations involving the transcription factor CBFA1 cause cleidocranial dysplasia. Cell, 89, 773–779. https://doi.org/10.1016/S0092-8674(00)80260-3

Murphy, M., Ahn, J., Walker, K. K., Hoffman, W. H., Evans, R. M., Levine, A. J., & George, D. L. (1999). Transcriptional repression by wild-type p53 utilizes histone deacetylases, mediated by interaction with mSin3a. Genes & Development, 13, 2490–2501. https://doi.org/10.1101/gad.13.19.2490

Murr, R., Vaisiare, T., Savan, C., Shukla, V., & Herceg, Z. (2007). Orchestration of chromatin-based processes: Mind the TRRAP. Oncogene, 26, 5358–5372. https://doi.org/10.1038/sj.onc.1210605

Nakagawa, T., Bulger, M., Muramatsu, M., & Ito, T. (2001). Multistep chromatin assembly on supercoiled plasmid DNA by nucleosome assembly protein-1 and ATP-utilizing chromatin assembly and remodeling factor. The Journal of Biological Chemistry, 276, 27384–27391. https://doi.org/10.1074/jbc.M101331200

Nei, Y., Obata-Ninomiya, K., Tsutsui, H., Ishiwata, K., Miyasaka, M., Matsumoto, K., …, Karasuyama, H. (2013). GATA-1 regulates the generation and function of basophils. Proceedings of the National Academy of Sciences of the United States of America, 110, 18620–18625. https://doi.org/10.1073/pnas.1311668110

Nicholas, J. C., Valentine, W., Kanwal, S., & Carter, B. D. (2003). Activation of the transcription factor NF-kappaB in Schwann cells is required for peripheral myelin formation. Nature Neuroscience, 6, 161–167.

Ninkovic, J., Steiner-Mezzadri, A., Jawerka, M., Akinci, U., Masserdotti, G., Petricca, S., … Götz, M. (2013). The BAFlower complex interacts with Pax6 in adult neural progenitors to establish a neurogenic cross-regulatory transcriptional network. Cell Stem Cell, 13, 403–418. https://doi.org/10.1016/j.stem.2013.07.002

Oliviero, G., Brien, G. L., Waston, A., Streubel, G., Jerman, E., Andrews, D., … Cagney, G. (2016). Dynamic protein interactions of the polycomb repressive complex 2 during differentiation of pluripotent cells. Molecular & Cellular Proteomics : MCP, 15, 3450–3460. https://doi.org/10.1074/mcp.M116.62240

Osafune, K., Takasato, M., Kispert, A., Asashima, M., & Nishinakamura, R. (2006). Identification of multipotent progenitors in the embryonic mouse kidney by a novel colony-forming assay. Development, 133, 151–161. https://doi.org/10.1242/dev.02174

Osorio, K. M., Lee, S. E., McDermitt, D. J., Waghmare, S. K., Zhang, Y. V., Woo, H. N., & Tumbar, T. (2008). Runx1 modulates developmental, but not injury-driven, hair follicle stem cell activation. Development (Cambridge, England), 135, 1059–1068. https://doi.org/10.1242/dev.012799

Papamichos-Chronakis, M., Watanabe, S., Rando, O. J., & Peterson, C. L. (2011). Global regulation of H2A.Z localization by the INO80 chromatin-remodeling enzyme is essential for genome integrity. Cell, 144, 200–213. https://doi.org/10.1016/j.cell.2010.12.021

Phelan, M. L., Sif, S., Narlikar, G. J., & Kingston, R. E. (1999). Reconstitution of a core chromatin remodeling complex from SWI/SNF subunits. Molecular Cell, 3, 247–253. https://doi.org/10.1016/S1097-2765(00)80315-9

Qiao, Y., He, H., Jonsson, P., Sinha, I., Zhao, C., & Dahlman-Wright, K. (2016). AP-1 is a key regulator of proinflammatory cytokine TNFalpha-mediated triple-negative breast cancer progression. The Journal of Biological Chemistry, 291, 5068–5079.

Ragoczy, T., Bender, M. A., Telling, A., Byron, R., & Groudine, M. (2006). The locus control region is required for association of the murine beta-globin locus with engaged transcription factories during erythroid maturation. Genes & Development, 20, 1447–1457. https://doi.org/10.1101/gad.1419506

Raymon, J. B., Takahashi, Y., Indjejian, V. B., Dannenberg, J. H., Catchpole, S., Watson, R. J., … Dynlacht, B. D. (2002). E2F mediates cell cycle-dependent transcriptional repression in vivo by recruitment of an HDAC1/mSin3B corepressor complex. Genes & Development, 16, 933–947. https://doi.org/10.1101/gad.969202

Reiter, F., Wienerroither, S., & Stark, A. (2017). Combinatorial function of transcription factors and cofactors. Current Opinion in Genetics & Development, 43, 73–81. https://doi.org/10.1016/j.gde.2016.12.007

Rodriguez, P., Bonte, E., Krijgsveeld, J., Koledziej, K. E., Guyot, B., Heck, A. J., … Strouboulis, J. (2005). GATA-1 forms distinct activating and repressive complexes in erythroid cells. The EMBO Journal, 24, 2354–2366. https://doi.org/10.1038/sj.emboj.7600702

Saito, M., & Ishikawa, F. (2002). The mCpG-binding domain of human MBD3 does not bind to mCpG but interacts with NuRD/Mi2 components HDAC1 and MTA2. The Journal of Biological Chemistry, 277, 35434–35439. https://doi.org/10.1074/jbc.M203455200

Sammons, M. A., Zhu, J., Drake, A. M., & Berger, S. L. (2015). TP53 engagement with the genome occurs in distinct local chromatin environments via pioneer factor activity. Genome Research, 25, 179–188. https://doi.org/10.1101/gr.181883.114

Sartorelli, V., & Caretti, G. (2005). Mechanisms underlying the transcriptional regulation of skeletal myogenesis. Current Opinion in Genetics & Development, 15, 528–535. https://doi.org/10.1016/j.gde.2005.04.015

Satrimafirah, P., Barman, H. K., Ahmad, A., Nishitoh, H., Nakayama, T., Fukagawa, T., & Takami, Y. (2016). RhAp48 is essential for viability of vertebrate cells and plays a role in chromosome
Schuettengruber, B., Bourbon, H. M., Di Croce, L., & Cavalli, G. (2017). Genome Regulation by Polycomb and Trithorax: 70 Years and Counting. Cell, 171, 34–57. https://doi.org/10.1016/j.cell.2017.08.002

Schuettengruber, B., & Cavalli, G. (2009). Recruitment of polycomb group complexes and their role in the dynamic regulation of cell fate choice. Development (Cambridge, England), 136, 3531–3542. https://doi.org/10.1242/dev.033902

Shen, X., Ranallo, R., Choi, E., & Wu, C. (2003). Involvement of actin-related proteins in atp-dependent chromatin remodeling. Molecular Cell, 12, 147–155. https://doi.org/10.1016/S1097-2765(03)00264-8

Shi, Y. J., Matson, C., Lan, F., Iwase, S., Baba, T., & Shi, Y. (2005). Regulation of LSD1 histone demethylase activity by its associated factors. Molecular Cell, 19, 857–864. https://doi.org/10.1016/j.molcel.2005.08.027

Simon, J. A., & Kingston, R. E. (2009). Mechanisms of polycomb gene silencing: Knowns and unknowns. Nature Reviews Molecular Cell Biology, 10, 697–708.

Singhal, N., Graumann, J., Wu, G., Araúzo-Bravo, M. J., Han, D. W., Greber, B., ... Schöler, H. R. (2010). Chromatin-Remodeling Components of the BAF Complex Facilitate Reprogramming. Cell, 141, 943–955. https://doi.org/10.1016/j.cell.2010.04.037

Speck, N. A., & Gilliland, D. G. (2002). Core-binding factors in haematopoeisis and leukaemia. Nature Reviews Cancer, 2, 502–513.

Squartini, M., Gorini, C., & Amati, B. (2006). Tip60 in DNA damage response and growth control: Many tricks in one HAT. Trends in Cell Biology, 16, 433–442. https://doi.org/10.1016/j.tcb.2006.07.007

Sridharan, R., & Smale, S. T. (2007). Predominant interaction of both Ikaros and Helios with the NuRD complex in immature thymocytes. The Journal of Biological Chemistry, 282, 30227–30238. https://doi.org/10.1074/jbc.M702541200

Steimle, J. D., & Moskowitz, I. P. (2017). TBX5: A key regulator of heart development. Current Topics in Developmental Biology, 122, 195–221.

Steinberg, T. M., Kahler, R. A., Li, X., & Westendorf, J. J. (2004). Histone deacetylase 3 interacts with runx2 to repress the osteocalcin promoter and regulate osteoblast differentiation. The Journal of Biological Chemistry, 279, 41998–42007. https://doi.org/10.1074/jbc.M403702200

Su, J., Sui, Y., Ding, J., Li, F., Shen, S., Yang, Y., ... Cai, Y. (2016). Human INO80/YY1 chromatin remodeling complex transcriptionally regulates the BRCA2- and CDKN1A-interacting protein (BCCIP) in cells. Protein & Cell, 7, 749–760. https://doi.org/10.1007/s13238-016-0306-1

Takaku, M., Grimm, S. A., Shimbo, T., Perera, L., Menafra, R., Stunnenberg, H. G., ... Wade, P. A. (2016). GATA3-dependent cellular reprogramming requires activation-domain dependent recruitment of a chromatin remodeler. GenomeBiology, 17, 36. https://doi.org/10.1186/s13059-016-0897-0

Tapsott, S. J. (2005). The circuitry of a master switch: Myod and the regulation of skeletal muscle gene transcription. Development, 132, 2685–2695. https://doi.org/10.1242/dev.01874

Taubert, S., Gorini, C., Frank, S. R., Parisi, T., Fuchs, M., Chan, H. M., ... Amati, B. (2004). E2F-dependent histone acetylation and recruitment of the Tip60 histoneactransferase complex to chromatin in late G1. Molecular and Cellular Biology, 24, 4546–4556. https://doi.org/10.1128/MCB.24.10.4546-4556.2004

Thomas, M. J., & Seto, E. (1999). Unlocking the mechanisms of transcription factor YY1: Are chromatin modifying enzymes the key? Gene, 236, 197–208. https://doi.org/10.1016/S0378-1119(99)00261-9

Trouche, D., Cook, A., & Kouzarides, T. (1996). The CBP co-activator stimulates E2F1/DP1 activity. Nucleic Acids Research, 24, 4139–4145. https://doi.org/10.1093/nar/24.21.4139

Tsukiyama, T., Daniel, C., Tamkun, J., & Wu, C. (1995). ISWI, a member of the SWI2/SNF2 ATPase family, encodes the 140 kDa subunit of the nucleosome remodeling factor. Cell, 83, 1021–1026.

Takaku, M., Grimm, S. A., Shimbo, T., Perera, L., Menafra, R., Stunnenberg, H. G., ... Wade, P. A. (2016). GATA3-dependent cellular reprogramming requires activation-domain dependent recruitment of a chromatin remodeler. GenomeBiology, 17, 36. https://doi.org/10.1186/s13059-016-0897-0

Steinberg, T. M., Kahler, R. A., Li, X., & Westendorf, J. J. (2004). Histone deacetylase 3 interacts with runx2 to repress the osteocalcin promoter and regulate osteoblast differentiation. The Journal of Biological Chemistry, 279, 41998–42007. https://doi.org/10.1074/jbc.M403702200

Schoenherr, C. J., & Anderson, D. J. (1995). The neuron-restrictive silencer factor (NRSF): A coordinate repressor of multiple neuron-specific genes. Science (New York, N.Y.), 267, 1360–1363.

Schroeder, T. M., Kahler, R. A., Li, X., & Westendorf, J. J. (2004). Histone deacetylase 3 interacts with runx2 to repress the osteocalcin promoter and regulate osteoblast differentiation. The Journal of Biological Chemistry, 279, 41998–42007. https://doi.org/10.1074/jbc.M403702200

Schoenherr, C. J., & Anderson, D. J. (1995). The neuron-restrictive silencer factor (NRSF): A coordinate repressor of multiple neuron-specific genes. Science (New York, N.Y.), 267, 1360–1363.
Westendorf, J. J., Zaidi, S. K., Cascino, J. E., Kahler, R., van Wijnen, A. J., Lian, J. B., … Li, X. (2002). Runx2 (Cbfa1, AML-3) interacts with histone deacetylase 6 and represses the p21CIP1/WAF1 promoter. *Molecular and Cellular Biology, 22*, 7982–7992. https://doi.org/10.1128/MCB.22.22.7982-7992.2002

Wu, J. I. (2012). Diverse functions of ATP-dependent chromatin remodeling complexes in development and cancer. *Acta Biochimica Et Biophysica Sinica, 44*, 54–69. https://doi.org/10.1093/abbs/gmr099

Wu, J. I., Lessard, J., Olave, I. A., Qiu, Z., Ghosh, A., Graef, I. A., & Crabtree, G. R. (2007). Regulation of dendritic development by neuron-specific chromatin remodeling complexes. *Neuron, 56*, 94–108. https://doi.org/10.1016/j.neuron.2007.08.021

Yan, Z., Cui, K., Murray, D. M., Ling, C., Xue, Y., Gerstein, A., … Wang, W. (2005). PBAF chromatin-remodeling complex requires a novel specificity subunit, BAF200, to regulate expression of selective interferon-responsive genes. *Genes & Development, 19*, 1662–1667. https://doi.org/10.1101/gad.1323805

Yao, Y. L., Yang, W. M., & Seto, E. (2001). Regulation of transcription factor YY1 by acetylation and deacetylation. *Molecular and Cellular Biology, 21*, 5979–5991. https://doi.org/10.1128/MCB.21.17.5979-5991.2001

Yoshida, T., & Georgopoulos, K. (2014). Ikaros fingers on lymphocyte differentiation. *International Journal of Hematology*, 100, 220–229. https://doi.org/10.1007/s12185-014-1644-5

Yoshida, T., Hazan, I., Zhang, J., Ng, S. Y., Naito, T., Snippert, H. J., … Georgopoulos, K. (2008). The role of the chromatin remodeler Mi-2-beta in hematopoietic stem cell self-renewal and multilineage differentiation. *Genes & Development, 22*, 1174–1189.

Yu, C., Cantor, A. B., Yang, H., Browne, C., Wells, R. A., Fujiwara, Y., & Orkin, S. H. (2002). Targeted deletion of a high-affinity GATA-binding site in the GATA-1 promoter leads to selective loss of the eosinophil lineage in vivo. *The Journal of Experimental Medicine, 195*, 1387–1395. https://doi.org/10.1084/jem.20020656

Yu, J., Li, Y., Ishizuka, T., Guenther, M. G., & Lazar, M. A. (2003). A SANT motif in the SMRT corepressor interprets the histone code and promotes histone deacetylation. *The EMBO Journal, 22*, 3403–3410. https://doi.org/10.1093/emboj/cdg326

Yu, M., Mazor, T., Huang, H., Huang, H.-T., Kathrein, K. L., Woo, A. J., … Cantor, A. B. (2012). Direct recruitment of polycomb repressive complex 1 to chromatin by core binding transcription factors. *Molecular Cell, 45*, 330–343. https://doi.org/10.1016/j.molcel.2011.11.032

Zahnow, C. A. (2009). CCAAT/enhancer-binding protein beta: Its role in breast cancer and associations with receptor tyrosine kinases. *Expert Reviews in Molecular Medicine, 11*, e12.

Zhang, J., Jackson, A. F., Naito, T., Dose, M., Seavitt, J., Liu, F., … Georgopoulos, K. (2011). Harnessing of the nucleosome-remodeling-deacetylase complex controls lymphocyte development and prevents leukemogenesis. *Nature Immunology, 13*, 86–94. https://doi.org/10.1038/ni.2150

How to cite this article: Nakagawa T, Yoneda M, Higashi M, Ohkuma Y, Ito T. Enhancer function regulated by combinations of transcription factors and cofactors. *Genes Cells*, 2018;23:808–821. https://doi.org/10.1111/gtc.12634