CHAPTER 12

Genetically altered cancer epigenome

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Contents

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1. INTRODUCTION

Cancer arises from abnormal expression and/or function of tumor suppressor genes and oncogenes, which may result from either genetic or epigenetic alterations. Eukaryotic genomic DNA is wrapped around the outside surface of the histone octamer to form nucleosomes, the repeating building blocks of chromatin. Chromatin is a dynamic structure and can be packed lightly or tightly. Chromatin structure impacts gene expression primarily by governing the genome accessibility for transcription factors and the transcriptional machinery. Covalent modifications of histones and DNA, nucleosome positioning, and long-distance chromatin interactions are critical determinants of active and repressive chromatin states. Cancer cells frequently exhibit an aberrant epigenome, notably epigenetic silencing of various tumor suppressor genes with vital functions in cancer-relevant signaling pathways, such as cell proliferation, apoptosis, and DNA repair [1,2].

In 2013 and 2014 large-scale cancer genomic studies (whole-exome and whole-genome sequencing) of nearly 5000 human tumor samples with matched normal tissues across 21 cancer types identified significantly mutated genes that drive malignancy [3,4]. The analyzed somatic mutations include substitutions and small insertions or deletions. Most cancer gene mutations in most patients occur at intermediate frequencies (2–20%) or lower. Statistically significant somatic mutations are found in a wealth of chromatin regulators that are directly involved in histone modifications, DNA methylation, nucleosome remodeling, and long-range chromatin interactions. Genetic alterations of these regulators are expected to disturb global epigenetic patterns and have the potential to deregulate numerous genes genome-wide (including tumor suppressor genes and oncogenes), which may catastrophically contribute to tumor initiation, progression, and metastasis. The findings illustrate a mechanistic link that leads from genetic mutations to altered epigenome [5,6].

2. HISTONE MODIFICATIONS

The amino-terminal tails of core histones protrude outward beyond the gyres of DNA. Many specific residues within the histone tails can undergo a diverse array of post-translational modifications, such as acetylation, methylation, and monoubiquitination, which are established or reverted by corresponding histone-modifying enzymes. These modifications may directly impact chromatin structure and/or serve as docking signals to recruit new chromatin-modifying or remodeling complexes that may further stabilize or reprogram the epigenetic landscape. Therefore, histone modifications are instrumental for the regulation of chromatin accessibility and dynamics, and affect essentially all DNA-templated processes, including gene transcription, replication, and repair. Deregulation of histone modifications may result in abnormal cell proliferation and survival and eventual development of cancer (Table 1).

Table 1 Histone-modifying complexes significantly mutated in cancer

Enzyme type	Mutated subunit	Substrate	Mutation prevalence in cancer
KMT	MLL1/KMT2A	H3K4	1% breast, 13% bladder, 3% combined
	MLL2/KMT2D	H3K4	26% bladder, 21% diffuse large B-cell lymphoma, 20% lung SCC, 15% head and neck, 6% combined, 4% medulloblastoma
	MLL3/KMT2C	H3K4	7% breast, 6% combined, 24% bladder, 15% lung adenocarcinoma, 7% head and neck
	MLL4/KDM2B	H3K4	2% combined, 14% endometrial
	SETD2/KMT3A	H3K36	12% kidney CCC, 4% combined, 2% glioblastoma, 6% bladder
	NSD1/KMT3B	H3K36	10% head and neck, 3% combined, 6% lung SCC
	EZH2/KMT6A[a]	H3K27	10% diffuse large B-cell lymphoma, 2% AML
KDM	UTX/KDM6A	H3K27me2/3	27% bladder, 2% combined, 2% head and neck, 2% AML
	SMCX/JARID1C/KDM5C	H3K4me2/3	7% kidney CCC, 2% combined
	ARID5B (complex with PHF2/JHDM1E/KDM7C)	H3K9me1/2	12% endometrial
DUB	BAP1	H2AK119ub1	11% kidney CCC, 2% combined
	ASXL1 (complex with BAP1)		2% combined, 3% AML, 5% lung SCC, 3% head and neck
	ASXL2		2% combined, 7% bladder
KAT	CBP/CREBBP/KAT3A	Core histones	24% diffuse large B-cell lymphoma, 3% combined, 12% bladder
	p300/EP300/KAT3B	Core histones	3% combined, 9% endometrial, 7% head and neck, 4% lung SCC

Acronyms: AML: acute myeloid leukemia; CCC: clear cell carcinoma; SCC: squamous cell carcinoma.
[a]Gain-of-function mutations.

2.1 Lysine methyltransferases (KMTs)

Histone methylation involves lysine and arginine residues. The major families of SET (**s**u(var)3–9, **e**nhancer-of-zeste (EHZ), **T**rithorax (Trx)) domain-containing proteins act as lysine methyltransferases (KMTs) to catalyze the methylation of particular lysine residues on histones H3 and H4 [7]. Lysine methylation occurs in multiple states, including mono-, di-,

or trimethylation. Different lysine methylation marks may be associated with distinct transcriptional readouts. Typically, H3 lysine 4 di- and trimethylation (H3K4me2/3) are marks of active transcription, whereas H3K9me2/3 and H3K27me2/3 indicate repressive chromatin.

2.1.1 MLL1-4

Mixed lineage leukemias (MLLs) are H3K4-specific methyltransferases and play important roles in the regulation of gene transcription, epigenetic modification, and tumorigenesis [8]. In mammal, there exist several MLL proteins, such as MLL1-4, which are capable of mono-, di-, and trimethylating H3K4. As H3K4me2/3 are associated with active transcription, MLLs are transcriptional coactivators [9].

MLL1 and MLL2 share a high degree of structural similarity and are the mammalian homologs of the *Drosophila* Trx protein. In *Drosophila*, the Trithorax group (TrxG) and the Polycomb group (PcG) proteins play a central role in the regulation of homeotic gene expression throughout development [10]. The two families of proteins positively and negatively regulate transcription, respectively. MLL1 is required for the H3K4 trimethylation and transcription of a small subset of genes, including developmental regulators, such as homeobox (Hox) genes [11]. MLL1 is perhaps best known for its involvement in leukemia [12]. Approximately 10% of all human acute leukemias harbor MLL1 chromosomal translocations. MLL1 translocations involve more than 60 different partner genes, many of which seem unrelated. A number of the most common MLL1 translocation partners are involved in transcriptional elongation, suggesting abnormal RNA polymerase II (Pol II) transcription elongation may be fundamental to MLL-induced leukemogenesis [13]. All MLL-fusion proteins retain the amino terminus of MLL1 that is responsible for chromatin association. Furthermore, in-frame fusion of MLL1 to a partner protein is required for cellular transformation. These observations suggest that MLL1 translocation-mediated leukemic pathogenesis is not due to a loss-of-function mechanism. MLL is also affected by other chromosomal abnormalities, including partial tandem duplications and genomic amplifications. All MLL1 rearrangements cause aberrantly increased and sustained expression of Hox genes, which disturbs hematopoietic differentiation and is central to leukemogenesis.

However, inactivating mutations of MLL1 and MLL2 have been uncovered in multiple types of solid tumors, suggesting that MLL1 and MLL2 possess tumor-suppressive function. In fact, the tumor suppressor Menin, which is mutated in multiple endocrine neoplasia type 1, directly interacts with the amino terminus of MLL1/MLL2 and is an essential component of both the MLL1 and MLL2 complexes. Deletion of Menin abolishes the majority of H3K4 trimethylation and gene expression on all Hox gene clusters [11]. Importantly, MLL1 activates expression of cyclin-dependent kinase inhibitors (CKIs) p27 and p18 in a Menin-dependent manner [14]. Inactivating Menin mutations lead to failed induction of these CKIs, which is likely to be an important oncogenic pathway in such endocrine tumors. Induction of cellular senescence by

oncogenic signals (e.g., Ras [rat sarcoma], Myc [myelocytomatosis]) functions as a barrier to cellular transformation. MLL1 is required for the induction of p16 (also a CKI and a tumor suppressor) by oncogenic Ras during oncogenic checkpoint response [15]. MLL2 is involved in several important cellular signaling pathways, including the p53 tumor suppressor [16]. These functions of MLL1 and MLL2 are of critical importance in the epigenetic regulation of the cell cycle and senescence, and may explain why they exert tumor suppressor activities.

MLL3 and MLL4 are the mammalian homologs of the *Drosophila* trithorax-related (Trr) gene [8]. In *Drosophila*, functions of Trr and Trx are not redundant, and each has specific genomic targets. Genome-wide binding studies demonstrated that Trr and MLL3/MLL4 are bound to distal regulatory elements and transcription start sites [17,18]. Monomethylated H3K4 (H3K4me1) is a general mark for enhancers [19]. MLL3 and MLL4 are involved in the implementation of H3K4 monomethylation on enhancers. Loss of MLL3 and MLL4 results in decreased H3K4me1 on the majority of enhancers [18]. H3K4me1 and acetylation of H3K27 are histone modifications that are highly enriched on active enhancers, whereas H3K4me1 and H3K27me3 mark inactive/poised enhancers. The MLL3 and MLL4 complexes specifically contain the H3K27 demethylase UTX (lysine-specific demethylase 6A). Impairment of MLL3/MLL4 also alters H3K27 acetylation at enhancer regions [17]. These studies reveal a direct role for MLL3/MLL4 and UTX in the transition of enhancers from inactive/poised to active status.

In *Drosophila*, both Trr mutant cells and UTX mutant cells similarly display an overgrowth phenotype, suggesting Trr and UTX restrict tissue growth [20]. In human, MLL3 has been identified as a tumor suppressor gene frequently altered in various tumors. Mutations of MLL3 and MLL4 are expected to cause malfunction of numerous enhancers. Deregulation of enhancer activity may cause aberrant expression of tumor suppressors and oncogenes, contributing to tumorigenesis. Moreover, the MLL3/MLL4 family members interact with tumor suppressor p53 and are involved in the p53-mediated DNA damage response [21].

2.1.2 SETD2 and NSD1

SETD2 (SET domain containing 2) and NSD1 (nuclear receptor binding SET domain protein 1) are histone H3K36 methyltransferases. SETD2 is mainly responsible for H3K36me3, and NSD1 preferentially for H3K36me1/2 [22]. H3K36 methylation is implicated in diverse processes, including gene transcription and DNA repair and recombination [23]. Altered placement of H3K36 methylation within the chromatin landscape can lead to a range of human diseases, including cancer. Mutations of SETD2 result in a global reduction of H3K36me3 in tumor cells [24]. In collaboration with other genetic lesions (e.g., MLL1 translocation), loss of SETD2 contributes to both initiation and progression of leukemia by enhancing the self-renewal potential of leukemia stem cells [25]. Therefore, the SETD2-H3K36me3 pathway represents a tumor-suppressive mechanism. SETD2 interacts with

p53 and regulates its transcription activity [26]. SETD2 is required for activation of ATM (ataxia telangiectasia mutated) by DNA double-strand breaks (DSBs) and for homologous recombination repair of DSBs [27,28]. SETD2-mutant cells exhibit impaired DNA damage signaling and fail to activate p53. Depleting SETD2 causes defective homologous recombination repair. In addition, the H3K36me3 mark is required in vivo to recruit the mismatch recognition protein complex [29]. Cells lacking SETD2 display microsatellite instability (MSI) and an elevated spontaneous mutation frequency, characteristic of DNA mismatch repair (MMR)-deficient cells. Loss-of-function mutations in NSD1 cause the Sotos overgrowth syndrome [30], but their connection to cancer remains poorly understood.

2.1.3 EZH2

Histone methyltransferase EZH2 (enhancer of zeste homolog 2) is the catalytic subunit of the Polycomb repressive complex 2 (PRC2) and is involved in repressing gene expression through di- and trimethylation of H3K27 [31]. EZH2 is a major proto-oncogene. EZH2 is overexpressed in several common solid tumor types, and is associated with advanced stages of disease and poor prognosis [32]. Moreover, the enzyme may be activated by mutations. The Y641 residue within the catalytic domain of EZH2 is a hotspot of mutations, especially in diffuse large B-cell lymphoma and follicular lymphoma [33]. Recurrent missense mutations at this site change substrate preferences of the mutant enzymes and increase H3K27me3, thereby representing gain-of-function mutations [34,35].

PcG proteins (including EZH2) can induce tumorigenesis in part through direct repression of critical tumor suppressor genes, such as p16-ARF (where ARF stands for alternate reading frame) and E-cadherin [36,37]. The p16-ARF locus encodes several well-established tumor suppressors and is frequently mutated or silenced in human tumors [38]. EZH2 mediates epigenetic silencing of p16 and is essential in cancer stem cells [39]. Expression of EZH2 and E-cadherin exhibits an inverse correlation in cancer, and E-cadherin expression is restored when EZH2 is depleted [37,40]. Pharmacological inhibition of EZH2 methyltransferase activity decreases global H3K27me3 levels, reactivates silenced PRC2 target genes, and markedly inhibits the growth of EZH2 mutant tumors [41,42].

Paradoxically, however, inactivating mutations in EZH2 have also been reported to promote myeloid disorders [43,44]. In accordance, recurrent K27 missense mutations in histone H3 and its variant H3.3 have been observed particularly in gliomas [45–48]. K27-mutated H3 or H3.3 tails function as a pseudosubstrate to aberrantly recruit the PRC2 complex and inhibit the enzymatic activity of EZH2. The dominant-negative effect of K27 mutations leads to a global reduction of H3K27me3 and aberrant gene activation. The dual role of EZH2 and H3K27 methylation in cancer suggests EZH2's pro- or anti-tumorigenesis function is probably context dependent.

2.2 Lysine demethylases (KDMs)

The Jumonji C (JmjC)-domain-containing enzymes can demethylate lysine residues and are the major histone demethylases [49]. The demethylases play critical roles in developmental processes and human diseases such as cancer.

2.2.1 UTX

UTX is a H3K27-specific demethylase (opposite to EZH2). UTX is inactivated by recurrent somatic mutations in a number of tumors, leading to increased H3K27 methylation [50]. Inactivation of UTX is considered the same as enhancing EZH2 activity. UTX is a specific subunit of the MLL3 and MLL4 complexes [17,18]. UTX, MLL3, and MLL4 are all frequently mutated in human cancers, suggesting deregulated enhancers may be an important mechanism underlying UTX tumorigenesis. Furthermore, mutations in UTX and MLL2 are mutually exclusive in urothelial carcinoma of the bladder [51], suggesting that mutations in the two genes may have similar downstream effects on carcinogenesis.

2.2.2 SMCX

SMCX (lysine (K)-specific demethylase 5C) is a member of the JARID1 (jumonji, AT-rich interactive domain 1) family of H3K4 demethylases [52] and is frequently mutated in renal cell carcinoma (RCC) [53]. SMCX has been identified as a target gene of hypoxia-inducible factor (HIF) in RCC cells to decrease H3K4Me3 levels [54]. Inactivation of SMCX promotes tumor formation in RCC [54]. Furthermore, another member of the JARID1 family, RBP2 (retinol binding protein 2), was firstly identified as a binding partner of the Rb tumor suppressor [55]. RBP2 also inhibits the oncogenic Notch signaling pathway and Notch-induced tumorigenesis by erasing the H3K4me3 mark at Notch target genes [56]. Given their homology, SMCX may function similarly as RBP2.

2.2.3 ARID5B

ARID5B (AT-rich interactive domain-containing protein 5B) is a DNA-binding protein and forms a complex with the histone H3K9 demethylase PHF2 [57]. The ARID5B-PHF2 complex acts as a transcriptional coactivator. PHF2 (PHD[polyhomeotic distal protein] finger protein 2) recognizes the active H3K4me3 mark. Once the ARID5B-PHF2 complex is recruited to target promoters, PHF2 mediates the demethylation of the repressive H3K9Me2 mark, facilitating transcriptional activation of target genes [57,58]. Defects in ARID5B may be a cause of susceptibility to transformation. However, it remains obscure how the ARID5B-PHF2 complex exhibits tumor-suppressive function.

2.3 Deubiquitinase (DUB)

2.3.1 BAP1-ASXL1/2

H3K27me3-marked repressive chromatin is recognized by Polycomb repressive complex 1 (PRC1), which possesses ubiquitin ligase activity and maintains the transcriptionally silenced

state by further monoubiquitinating K119 of histone H2A (H2AK119Ub1) [59]. Therefore, deubiquitination of H2AK119Ub plays a critical role in chromatin modulation and transcriptional regulation. The Polycomb repressive deubiquitinase (PR-DUB) complex specifically mediates deubiquitination of H2AK119ub1 [60]. This deubiquitinating complex is at least composed of BAP1 (BRCA1 [breast cancer 1, early onset] associated protein-1) and ASXL1 (additional sex combs like transcriptional regulator 1), in which the BAP1 enzyme is the catalytic subunit. ASXL1 is frequently mutated in most types of myeloid malignancies [61–63]. Mutations in ASXL1 result in loss of H3K27me3 [64]. ASXL2 may share similar biochemical functions with ASXL1. BAP1 is deleted in some human cancers and is an established tumor suppressor gene [65,66]. Besides ASXL1, BAP1 is associated with other protein complexes. For instance, BAP1 interacts with the BRCA1 tumor suppressor, and exerts growth inhibitory effects in a BRCA1-dependent manner [67].

2.4 Histone acetyltransferases (HATs)

2.4.1 CBP and p300

Histone acetyltransferases (HATs) and deacetylases (HDACs) play a pivotal role in modifying chromatin structure and gene expression. HATs acetylate lysine residues in histone tails and loosen chromatin structure, thereby increasing accessibility of regulatory proteins to DNA. Acetylated lysine may also serve as recruiting marks to attract chromatin regulatory complexes [68]. By contrast, HDACs condense chromatin and repress gene transcription. Aberrant histone acetylation is associated with the initiation and progression of cancer. Histone acetyltransferases CBP (CCAAT enhancer-binding protein) and p300 are close homologs and can acetylate multiple lysine sites of core histones. They function as transcriptional coactivators of various sequence-specific transcription factors that are involved in cell proliferation, differentiation, and apoptosis. Somatic mutations of p300 and CBP have been detected in a number of malignancies. Chromosomal translocations frequently target CBP and p300 in acute leukemia, whereas loss-of-function mutations in the two genes have been identified in solid tumors, including colorectal and breast carcinomas [69]. The inactivating mutations result in truncated protein products or amino-acid substitutions in critical protein domains, and are often associated with inactivation of the second allele. Recurrent mutations at D1399 of the p300 catalytic domain are observed, which are likely to affect the catalytic activity of this HAT [70]. Mutations in CBP and p300 can impair histone acetylation and transcriptional regulation of their targets. These factors are involved in critical tumorigenic pathways (including p53 and Rb) [69,71]. Their tumor-suppressive activity has been confirmed in a mouse model [69].

3. DNA METHYLATION

DNA methylation is a common epigenetic modification in chromatin. In cancer, hypermethylation of CpG islands is a well-recognized epigenetic event. Hypermethylation of CpG island promoters leads to repressive histone modifications and gene silencing,

which occurs at numerous tumor suppressor genes [1]. The cancer genome is also characterized by global hypomethylation at repetitive and gene-body sequences. Hypomethylation of DNA loosens chromatin and causes chromosomal instability. Therefore, DNA methylation has a profound impact on transcription and genome stability, and is significantly associated with cell growth, differentiation, and transformation.

3.1 DNA methyltransferase (DNMT)

3.1.1 DNMT3A

DNA methylation is established by DNA methyltransferases (DNMTs), which generate 5-methylcytosine (5mC) in CpG dinucleotides. DNMT3A is a de novo DNA methyltransferase. A variety of inactivating mutations in DNMT3A, including missense, nonsense, frame shift, and splice-site mutations, have been documented in human cancer [1]. While these mutations occur throughout various domains of DNMT3A, the majority of mutations in acute myeloid leukemia (AML) are heterozygous and specifically alter a single amino acid, R882, in the catalytic domain [72]. DNMT3A R882 hotspot mutations severely impair the DNA methyltransferase enzymatic activity. Moreover, as DNMT3A forms a tetrameric complex with other DNMT3 [73], the R882 mutants are capable of interacting with wild-type DNMT3, thereby inhibiting their ability to methylate DNA [74,75]. Therefore, DNMT3A R882 mutants, in addition to being hypomorphic, exert dominant-negative effects. These mutations induce focal hypomethylation at specific CGs throughout AML cell genomes and may cause abnormal activation of oncogenic genes. Indeed, DNMT3A R882H mutation was reported to increase the CDK1 (cyclin-dependent kinase 1) expression and enhance cell-cycle activity, thereby contributing to leukemogenesis [76].

3.2 5mC hydroxylase

3.2.1 TET2 and IDH1/2

TET2 is one of the three enzymes of the TET (ten-eleven translocation) family, which are evolutionarily conserved dioxygenases that catalyze the oxidization of 5mC to 5-hydroxymethyl-cytosine (5hmC) and promote DNA demethylation [77]. Loss-of-function mutations in TET2 have been discovered in myeloid malignancies and are implicated in the development of cancers. TET2 mutations reduce the global 5hmC levels [78]. Inactivation of TET2 likely alters genomic 5hmC and 5mC patterns and disrupts gene regulation. Analysis of TET2-deficient mice demonstrates that TET2 functions as a dose-dependent tumor suppressor, as TET2 haploinsufficiency initiates myeloid and lymphoid transformations [79].

Many chromatin-modifying enzymes depend on specific metabolites. For example, TET and Jmjc (Jumonji C) family enzymes use α-ketoglutarate (α-KG) as an essential cosubstrate. In this regard, abnormal metabolism may impact epigenome. Isocitrate dehydrogenases (IDHs) are metabolic enzymes that convert isocitrate to α-KG through oxidative decarboxylation. Recurrent hotspot missense mutations in IDH1 and IDH2 are frequently found in

glioma and AML. These mutations occur at a single amino acid residue of IDH1 (R132) and IDH2 (R140). Only a single copy of the genes is mutated in tumors. Groundbreaking studies have demonstrated that the tumor-derived IDH mutations are neomorphic: the IDH mutants acquire new enzymatic activity and are able to convert α-KG into (R)-2-hydroxyglutarate (2HG) [80,81]. 2HG inhibits α-KG-dependent epigenetic regulators (e.g., TET, Jmjc) and causes histone and DNA hypermethylation. IDH mutants induce global DNA hypermethylation and a hypermethylator phenotype [82,83]. In AML, IDH mutations are mutually exclusive with mutations in the α-KG-dependent TET2, and TET2 loss-of-function mutations cause similar epigenetic defects as IDH mutants.

Mutant IDHs can significantly increase histone methylation as well, presumably through 2HG-mediated inhibition of Jmjc histone demethylases including KDM4C (lysine (K)-specific demethylase 4C) [84]. Collectively, 2HG functions as an oncometabolite, and its excess accumulation contributes to tumor formation.

4. NUCLEOSOME REMODELING

Nucleosomes block access to DNA and impede the initiation and elongation of transcription. To activate transcription, nucleosomes need to be repositioned or removed to expose DNA sequence for binding of transcription factors and RNA Pol II. Nucleosome remodeling is a major means by which the cell modulates nucleosome mobility. This is accomplished by chromatin-remodeling complexes that use ATP hydrolysis to shuffle nucleosomes around and to replace or remove them from chromatin [85]. There are four classes of chromatin remodelers: SWI/SNF (SWItch/Sucrose NonFermentable), CHD (chromodomain helicase DNA-binding protein), ISWI (imitation SWI), and INO80. SWI/SNF and CHD-type remodelers are frequently mutated in human cancer (Table 2).

4.1 The SWI/SNF complexes

SWI/SNF complexes can remodel the chromatin structures by sliding nucleosomes [86] and can either eject or insert histone octamers [87]. SWI/SNF chromatin remodeling complexes are diverse assemblies of at least 14 subunits (a single subunit may be encoded by multiple genes) [88]. SWI/SNF complexes function as tumor suppressors in human malignancies [89]. Recurrent loss-of-function mutations in genes encoding various subunits of the SWI/SNF complexes have been found in a wide spectrum of cancer types [3,4,88]. The SWI/SNF complex has been identified as the most frequently mutated chromatin regulatory complex in cancer.

4.1.1 BRG1

BRG1 (Brahma-related gene 1) is one of the catalytic ATPase subunits in the SWI/SNF complexes. The other homologous BRM (SMARCA2 SWI/SNF-related,

Table 2 Nucleosome remodeling complexes mutated in cancer

Nucleosome remodeler	Mutated subunit	Mutation prevalence in cancer types
SWI/SNF	BRG1/SMARCA4	9% lung adenocarcinoma, 3% combined, 6% esophageal
	ARID1A/Baf250	33% endometrial, 25% bladder, 9% colorectal, 7% lung, 4% kidney CCC, 2% breast, 5% combined
	ARID2/Baf200	3% combined, 8% melanoma, 6% colorectal, 5% lung adenocarcinoma
	SNF5/SMARCB1/Baf47	7% rhabdoid, 2% esophageal, 1% combined
	PBRM1/Baf180	35% kidney CCC, 4% combined, 5% endometrial
NuRD	CHD4/Mi-2β	3% combined, 15% endometrial
CHD8	CHD8	9% GBM, 2% combined

matrix-associated, Actin-dependent regulator of chromatin, subfamily a, member 2) is present in the SWI/SNF complexes mutually exclusively with BRG1. Both BRG1 and BRM are able to reposition the nucleosome in vitro [90]. Although BRG1- and BRM-containing complexes show some redundancy, they may function distinctively [90]. Notably, BRG1-deficient mice are embryonic lethal, while BRM-deletion mice are viable [91]. In human cancer, BRG1 seems to be one of the most frequently mutated subunit genes, whereas the *BRM* gene is rarely mutated. The BRG1 subunit is either lost or mutated in a significant proportion of human primary non-small-cell lung cancer (NSCLC) samples [92]. It has also been found to be mutated in medullobalstoma [93], pancreatic cancer, breast cancer prostate cancer [94], and rhabdoid tumors [95]. Reduced BRG1 expression level can also drive tumorigenesis as evidenced by the fact that 10% BRG1 heterozygous mice develop mammary tumors [91]. Recently, it was shown that BRG1 binds to Myc (avian myelocytomatosis viral oncogene homolog) and Myc-target promoters to antagonize Myc activity and promotes cell differentiation in cancer cell lines and primary tumors [96]. Inactivation of BRG1 enables cancer cells to maintain the undifferentiated gene expression and prevents its response to environmental stimuli [96]. More recently, loss of BRG1 is shown to cooperate with oncogenic Kras (Kirsten rat sarcoma) to form cystic neoplastic lesions that resemble human intraductal papillary mucinous neoplasia (IPMN) [97]. Mechanistically, depletion of BRG1 leads to nucleosome landscape change genome-wide in vivo, highlighting its role in regulating chromatin structure and transcription [98]. Given its important role in controlling gene expression, inactivation of BRG1 can lead to aberrant expression of tumor suppressor genes and oncogenes.

4.1.2 ARID1A

ARID1A (AT-rich interactive domain 1A) and its paralog ARID1B (AT-rich interactive domain 1B) associate with other proteins to form the BRG1-associated (BAF) complexes in a mutually exclusive manner. ARID1A gene is frequently deleted in cancer [99]. Moreover, mutations in ARID1A were identified in various types of cancers. Fifty percent of ovarian clear cell carcinomas (OCCCs) and 30 percent of endometrioid carcinomas have mutations in ARID1A [100,101]. Mutations were also found in gastric carcinoma [99], esophageal adenocarcinoma [102], pediatric Burkitt lymphoma [103], medulloblastomas [93], breast cancers, and lung cancers, indicating its tumor suppressor activity in various cancer types [104]. ARID1A contains an AT-rich interaction domain (ARID) that binds to DNA without sequence specificity [105] and increases the BAF affinity to chromatin [106]. It is possible that mutations in the ARID domain disrupt the ARID-DNA interaction, thus abolishing its tumor suppression activity. ARID1A interacts with sequence-specific transcription factors, such as nuclear hormone receptors and p53, through its carboxyl-terminal domain and is required for the transcription activity of these transcription factors [107–109]. ARID1A can repress cellular proliferation in ovarian cancer [109], breast cancers [110], and gastric cancer [111]. Functional knockdown of ARID1A in these cancer cells enhances the proliferation rate. ARID1A regulates cell cycle by targeting BAF complexes directly to Myc promoter, whose expression is critical for p21 induction [112]. ARID1A physically interacts with p53 and they co-occupy the promoter of p21. Depletion of ARID1A resulted in reduced BRG1 binding at the p21 promoter and diminished p21 expression [109]. PIK3CA (phosphatidyl-inositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) mutations and ARID1A mutations are often observed hand-by-hand in ovarian clear cell carcinoma [100,113], suggesting that ARID1A mutations may cooperate with PI3K/Akt (phosphatidyl-inositol-4,5-bisphosphate 3-kinase/v-Akt murine thymoma viral oncogene homolog 1) pathway to promote cancer development. ARID1A can also help to maintain genome stability by ensuring proper chromosome segregation [114] and facilitating DNA damage repair [115].

4.1.3 ARID2

AT-rich interaction domain 2 (ARID2) was initially identified in the PBAF (Polybromo-associated BAF) complex [116]. ARID2 and ARID1A/B are mutually exclusive subunits occupying one position in the SWI/SNF complex. ARID2 is mutated in hepatocellular carcinoma [117]. Recently, ARID2 is identified as a new cancer driving gene in melanoma [118]. ARID2 is also frequently mutated in colorectal cancer as identified by exome sequencing [119]. ARID2 is mutated in 5% of non-small-cell lung cancers, making it one of the most frequently mutated genes in this cancer type [120]. Most of these mutations are inactivating mutations, suggesting that ARID2 is a potential tumor suppressor. ARID2 may help maintain the PBAF complex integrity, as depletion

of ARID2 reduces the protein levels of other subunits of the PBAF complex, presumably due to stoichiometric disturbance [121]. Depletion of ARID2 also diminishes the transcription of interferon-α-induced IFITM1(interferon-induced transmembrane protein 1), whose expression is critical for interferon-induced antiproliferative activity in hepatocellular carcinoma cells [122]. ARID2-deficient cells thus gain uncontrolled cell proliferation.

4.1.4 SNF5

SNF5 (sucrose nonfermenting factor gene number 5) is a highly conserved core subunit in the SWI/SNF complexes [90]. It has been shown to be required for the recruitment of SWI/SNF complexes to specific genes [123]. It is inactivated by biallelic mutations and/or loss of heterozygosity (LOH) in virtually all malignant rhabdoid tumors (RTs), an aggressive set of pediatric malignancies, and in a few other rare cancers [89]. In mouse models, 30% of Snf5-heterozygous mice develop sarcomas that are similar with human RTs [124,125]. Conditional inactivation of the other allele renders a cancer phenotype of full penetrance at a median onset of only 11 weeks [126].

Loss of SNF5 activates genes associated with cell proliferation, reminiscing its tumor suppressor activity [127]. SNF5 is shown to physically interact with p53, and SNF5 is recruited to p53-dependent promoters in vivo and is necessary for p53-mediated transcriptional activation [128]. Loss of p53, in addition to loss of SNF5, accelerates tumor formation [127]. Interestingly, SNF5 interacts with the MLL3 histone methyltransferase and facilitates its recruitment to chromatin [129]. Given that MLL3 is a primary H3K4me enhancer mark writer [18], it is not surprising that SNF5 is associated with gene activation. Consistent with its role in gene activation, SNF5 interacts with RNA Pol II complex containing acetyltransferases CBP and p/CAF(p300/CBP Associated Factor) [130]. As the SWI/SNF complexes and Polycomb play antagonistic roles in *Drosophila* development, mammalian SNF5 and EZH2 also exhibit antagonism toward each other [131]. Loss of the SNF5 leads to elevated expression of EZH2, and inactivation of EZH2 blocks tumor formation driven by Snf5 deficiency in mouse models.

4.1.5 PBRM1

BAF180 is composed of six tandem bromodomains that can recognize acetylated histones, two bromo-adjacent homology (BAH) domains needed for protein–protein interaction, and a high-mobility group (HMG) for binding DNA. BAF180 is a unique subunit in the polybromo/BRG1-associated factor (PBAF) complex, suggesting that it provides selective activity to this class of SWI/SNF remodelers. Indeed, it is implicated in recruiting PBAF complexes to specific loci [132]. Tumor suppressor VHL (von Hippel-Lindau) is the most frequently mutated gene in RCCs. Intriguingly, PBRM1 (polybromo 1), which encodes BAF180, is found to be mutated in 41% of the RCCs,

making it a highly mutated gene, second only to VHL [133]. BAF180 is mutated in breast cancer, and it is a critical regulator of CKI p21 induction [134]. BAF180 is shown to be a critical regulator of p53 and p53-induced replicative senescence as well [135]. Recently, a study demonstrated that BAF180 is required for centrometric cohesion. Cells without cohesion undergo genome instability followed by DNA damage [136]. Thus, protecting genome from instability is another mechanism for BAF180's tumor suppressor activity.

4.2 The CHD family of chromatin remodelers

4.2.1 CHD4

The nucleosome remodeling and histone deacetylase (NuRD), also known as Mi-2 complex, is an ATP-dependent chromatin remodeling complex [137]. NuRD complex remodels chromatin structure and thus regulates gene transcription [85]. This complex is composed of six core subunits: CHD3 (also known as Mi-2α) and CHD4 (also known as Mi-2β); HDAC1 and HDAC2; methyl-CpG-binding domain 2 (MBD2) and MBD3; metastasis-associated gene1 (MTA1), MTA2, and MTA3; retinoblastoma-binding protein 4 (RBBP4) and RBBP7; and GATAD2A (GATA zinc finger domain-containing protein 2A) and GATAD2B subunits. Among them, CHD3 and CHD4 have the ATP-dependent chromatin remodeling activity; HDAC1 and HDAC2 possess the protein deacetylation activity. Nonenzymatic MBD and MTA subunits are shown to target the complex to methylated DNA. The rest of the components of the NuRD complex are thought to provide structural support and serve as protein–protein interaction intermediates [138].

Whole-exome sequencing of uterine serous carcinoma revealed frequent mutations in CHD4 [139]. Another study identified somatic mutations in CHD4 in 17% of endometrial tumors [140]. Although most mutations identified are loss-of-function mutations, NuRD complex can either suppress or promote tumorigenesis depending on the cellular context. For example, CHD4 and HDAC1 are shown to interact with DNA methyltransferases 1 (DNMT1) physically and co-occupy hypermethylated tumor suppressor gene promoters. NuRD complex cooperates with DNMT1 to maintain the silencing of several negative regulators of the oncogenic Wnt (wingless-type MMTV integration site family) signaling pathways, thus contributing to tumorigenesis in colon cancer [141]. Recently, CHD4 is shown to interact with ZFHX4 (zinc finger homeobox 4), a transcription factor that is required to maintain tumor-initiating cell phenotype in glioblastoma. ZFHX4 and CHD4 colocalize at many genomic sites, suggesting that CHD4-mediated chromatin remodeling activity is critical to maintain glioblastoma phenotype [142]. Conversely, in breast cancer, ZIP (zinc finger, CCCH-type with G patch), a zinc finger, and G-patch domain-containing protein preferentially interacts with CHD3 and CHD4 subunits of the NuRD complex to suppress genes associated with cell proliferation, survival, and migration [143].

NuRD complex's role in maintaining genome stability is well established. Loss of CHD4 expression has been observed in gastric and colorectal cancer cases that are marked by genome instability [144]. Knockdown of CHD4 leads to cell-cycle arrest at G1/S transition phase, degradation of CDC25A (cell division cycle 25A), and accumulation of p21 [145,146]. NuRD complex is also well known as an integral component of DNA repair machinery. CHD4-deficient cells exhibit hypersensitivity to DNA damage, following ionizing radiation exposure, and display an increased number of unrepaired breaks at DNA damage sites [147].

4.2.2 CHD8

CHD8 is also a member of the chromodomain helicase (CHD) family. CHD8 is composed of two amino-terminal chromodomains, an SNF2-like helicase/ATPase domain, and two uncharacterized BRK domains. Mutations in CHD8 were identified in 35% of the gastric cancers and 28% of the colorectal cancers. These mutations lead to a loss of CHD8 expression [144]. CHD8 is also significantly mutated in glioblastoma [3]. CHD8 was initially shown to interact with β-catenin, a key oncogenic component of the canonical Wnt signaling pathway, and repress β-catenin target gene expression. ATP-dependent chromatin remodeling activity of CHD8 is critical to the repression of β-catenin-targeted gene expression [148]. More recently, CHD8 is shown to promote the association of β-catenin and histone H1, forming a trimeric complex on chromatin that is required for inhibition of β-catenin-dependent transactivation [149]. In a similar mechanism, CHD8 suppresses p53-mediated transactivation and apoptosis through histone H1 recruitment during embryogenesis [150]. CHD8 was copurified with MLL histone-modifying complexes. Depletion of CHD8 resulted in a loss of MLL activity and H3K4me3 at the HOXA2 (homeobox A2) promoter [151]. However, the significance of this interaction in cancer development is still unclear. Another notable partner of CHD8 is CTCF, an insulator protein that plays a critical role in gene regulation and high-order genome organization [152]. CHD8 colocalizes with CTCF at the differentially methylated region (DMR) of H19, the locus control region of β-globin, and the promoter region of BRAC1 and the Myc genes. Ablation of CHD8-affected CTCF-dependent insulator activity at those loci indicates a role of CTCF-CHD8 complex in insulation and epigenetic remodeling [152].

5. GENOME ORGANIZATION

5.1 CTCF genome organizer and the cohesin complex

CTCF (CCCTC-binding factor) is a multiple zinc finger protein that exerts diversified functions under different genomic contexts. CTCF was first isolated and cloned on the basis of its ability to bind to highly divergent 50–60 bp sequences within the promoter region of the chicken Myc gene [153]. Subsequent studies showed that CTCF can act

both as a transcriptional repressor and activator [154–156]. In addition, CTCF is well known as an insulator protein that possesses enhancer blocking function and barrier function [157]. Interestingly, recent studies show that CTCF can help to tether distal enhancers to their cognate promoters [158]. Moreover, 79% of long-range interactions between distal elements and promoters are not blocked by the presence of CTCF binding sites sitting in between [159]. This is in contrast to the traditional view of CTCF as an insulator protein.

Apart from its role in transcriptional regulation, perhaps the most famous role of CTCF is its genome organizer function [157,160]. Hi-C experiments revealed that the human genome is organized into megabase-sized topological domains [161]. Interestingly, CTCF is found to be enriched in the domain boundaries. However, CTCF binding alone is not sufficient to demarcate the domain boundaries, as only 15% of CTCF binding sites are located in the domain boundaries [161]. Additional factors such as cohesin might be also required at the topological domain boundaries [162,163]. However, cohesin and CTCF may differentially affect chromatin architecture [164]. Depletion of cohesin generally disrupts local chromatin interactions within the topological domains while keeping outer topological domains intact. In contrast, depletion of CTCF both decreases the intradomain interactions and simultaneously increases the interdomain interactions, suggesting that CTCF plays a dominant role in shaping the topological domain structure [164].

Various findings indicate that CTCF is a major tumor suppressor gene. CTCF is highly mutated in endometrial cancer and breast cancer [3]. Heterozygous deletion or mutation of CTCF was observed in leukemia [165]. Genome-wide ChIP-seq analysis revealed tens of thousands of binding sites for CTCF, indicating its wide-range regulatory function in the genome [166]. Mutations that reside in the 11 zinc finger region affect the binding specificity to DNA sequences [167]. Disruption of CTCF binding at specific gene loci can lead to aberrant expression of cancer-related genes. For example, tumor-derived CTCF mutants lost the binding affinity to growth-regulatory genes such as Myc, ARF and Igf2 (insulin-like growth factor 2) [168]. Deregulation of these genes may contribute to malignant tumor phenotypes. It is proposed that CTCF integrity may be important in controlling tumor angiogenesis [169,170]. Zinc-finger-mutated CTCF lost the binding affinity at the VEGFA (vascular endothelial growth factor A) locus, which encodes a prominent proangiogenic growth factor. Cancer cells harboring mutated CTCF thus are sensitized to hypoxia induction and gain increased angiogenic activity [169]. Conceivably, mutations in CTCF binding sites can also alter CTCF binding affinity and lead to unfavorable outcomes. Mutations in CTCF binding sites at the Igf2/H19 locus have been identified in patients with Beckwith-Wiedemann syndrome, an overgrowth disorder predisposing patients to pediatric cancer, suggesting that functional loss of CTCF binding may contribute to this disease [171]. Reduced expression level of CTCF can cause cancer as well. Hemizygous CTCF knockout mice are

susceptible to spontaneous, radiation-, and chemical-induced cancer and exhibit a genome-wide perturbation in DNA methylation [172]. This evidence demonstrates that CTCF haploinsufficiency predisposes to cancer by losing CTCF-mediated epigenetic stability [172].

The cohesin complex consists of SMC1A (structural maintenance of chromosome protein 1A), SMC3 (structural maintenance of chromosome protein 3), RAD21/SCC1 (sister-chromatid cohesin protein 1), and SCC3 (sister-chromatid cohesin protein 3) (encoded by STAG-1, -2, and -3). It mediates sister chromatid cohesion to ensure accurate chromosome segregation during mitosis. Cohesin also collaborates with CTCF to control gene expression through long-distance DNA looping [173,174]. Recurrent mutations in cohesin subunits have been identified in myeloid neoplasms [175] and bladder cancer [176]. While inactivation of *STAG2* (cohesin subunit SA-2) expectedly causes chromatid cohesion defects and aneuploidy in Ewing's sarcoma, glioblastoma, and melanoma [177], it is not associated with aneuploidy in bladder cancer [178]. In addition, acute myeloid leukemias with mutations in *STAG2* and other cohesin genes have completely normal karyotypes [179]. These observations suggest that cohesin may have tumor-suppressive function independent of mitotic regulation, which may involve CTCF-related genome organization and gene regulation.

6. CONCLUDING REMARKS

Cancer genome sequencing studies have identified driver mutations in chromatin regulatory proteins, which cause deregulation of histone modifications, DNA methylation, nucleosome remodeling, and high-order chromatin organization. As most chromatin regulators are normally associated with thousands of target genes and loci throughout the genome, their disruption is likely to have profound effects on global gene expression and contribute to various forms of malignancies. Although in most cases, the precise mechanisms linking mutations in a particular chromatin regulator to corresponding neoplasms have yet to be fully deciphered, these studies demonstrate that genetic alterations give rise to epigenetic aberrations, thereby illustrating a genetic basis for altered cancer epigenome.

Unlike genetic changes, epigenetic alterations are in principle reversible by pharmacologic manipulation. Although the whole-exome analysis uncovers predominantly loss-of-function mutations, oncogenic activating mutations are also detected in a few chromatin regulators (e.g., EZH2, IDH1/2). Other gain-of-function alterations may be achieved by overexpression, amplification, and chromosomal translocations [180]. The epigenetic abnormalities resulting from deregulated chromatin-modifying enzymes offer promising opportunities for cancer therapy [2,181]. Indeed, small molecule inhibitors targeting DNA methylation and certain forms of histone methylation have led to tangible clinical benefits.

However, epigenetic gene regulation is complex. Each chromatin regulator may affect numerous genes genome-wide and is likely to be pleiotropic. It remains a challenging task to understand the many downstream effects when a chromatin factor is mutated or therapeutically targeted in cancer. Presumably depending on cellular context, a particular chromatin regulator or epigenetic modification may function as an oncogene in one setting but a tumor suppressor in other circumstances. This is exemplified by the dual roles of EZH2 and H3K27me3, and inactivating mutations in both DNMT3A and TET2 that may have opposite effects on DNA methylation. It is difficult to predict potential outcomes when a defined drug is systematically administered because different tissues may respond differently. Cautions should be taken for long-term treatment with epigenetic inhibitors.

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