Chapter

Chromatin Dynamics: Chromatin Remodeler, Epigenetic Modification and Diseases

Guofei Cui, Qing Dong, Kexin Gai and Shaohua Qi

Abstract

The gene transcription patterns are regulated in response to extracellular stimuli and intracellular development programs. Recent studies have shown that chromatin dynamics which include nucleosome dynamics and histone modification play a crucial role in gene expression. Chromatin dynamic is regulated by chromatin modification enzymes including chromatin remodeling complex and histone posttranslational modifications. Multiple studies have shown that chromatin dynamics dysregulation and aberrant and histone modifications resulted in the occurrence of various diseases and cancers. Moreover, frequent mutations and chromosomal aberrations in the genes associated with subunits of the chromatin remodeling complexes have been detected in various cancer types. In this review, we highlight the current understanding of orchestration of nucleosome position, histone modification, and the importance of these properly regulated dynamics. We also discuss the consequences of aberrant chromatin dynamic which results in disease progression and provides insights for potential clinic applications.

Keywords: chromatin dynamic, chromatin remodeler, epigenetic modification, gene regulation

1. Introduction

In eukaryotic cells, chromatin is the genetic material carrier which packaged of DNA with histone and non-histone proteins. The simplest form of chromatin structure is the nucleosome core particle. Each nucleosome is composed of 147 bp of DNA wrapped around an octamer of histone proteins (two copies each of core histones H2A, H2B, H3, and H4) plus a linker histone (H1) involved in higher-order chromatin compaction [1]. In general, chromatin assembly limits the accessibility of genomic sequences, and thus it creates inherent barriers for nuclear events such as transcription, DNA replication, and DNA repair. Consequently, chromatin structure must be regulated dynamically, and its compaction and assembly are regulated by multiple mechanisms, including DNA methylation, histone post-translational modification, histone variant incorporation, chromatin remodeling, histone eviction, and non-coding RNA pathways [2–4]. During the DNA replication, DNA damage repair, and transcription process, the assembly and disassembly of chromatin structure stay on a dynamic and balanced status-first, the core histones in front of the replication fork or

activated transcription region need to be released from the nucleosome to allow the DNA replication and RNA polymerase II machinery to passage and then reassemble again after these processes are completed, as the events of DNA replication and RNA transcription occurring, the chromatin assembly and reassembly also keep a dynamic and balanced process [5–8]. Meanwhile, the nucleosome position is not randomly arranged; instead, it is regulated by chromatin remodeling complex to either condense or loosen status at different loci of the nucleus. Chromatin is compacted into higher-order structures-named chromosomes, including loosely packaged euchromatin that is open and functionally active and more condense packaged status that is relatively repressive heterochromatin and maintains genomic integrity [9–11].

The chromatin remodeling complexes are the second major class of chromatin regulators. They are involved in different biological events such as DNA replication and transcription, through altering the components, positions, and numbers of nucleosomes around the gene. It also involves diverse modulators and protein domains for the various processes: nucleosome organization, disorganization, ejection, or changes in nucleosome composition [12, 13]. These chromatin remodeler complexes constitute a highly related family of multi-subunit complexes, and the core catalytic subunit is comprised of the ATPase domain that hydrolyzes ATP. Therefore, the chromatin remodeler complexes are ATP-dependent chromatin-remodeling enzymes that use the energy of ATP hydrolysis to remodel nucleosomes. Other substrate recognizing subunits direct the nucleosome sliding, facilitate the access of transcription factors to nucleosome DNA, change the DNA topology on specific nucleosomes targets, and generate distinct remodeling outcomes [14, 15].

Here, we focus on the studies on the related chromatin remodeling complexes and epigenetic modification and summarize recent advanced knowledge on the power of chromatin remodelers and its associated dynamically epigenetic regulation. Moreover, we explored the correlations between chromatin dynamic regulation and diseases progression, highlighted the importance of various chromatin modifiers targets for disease therapy. We also discuss emerging evidence of the new roles for chromatin regulators in developmental transitions in the future clinic application. Given that most knowledge about the chromatin remodeling complexes are described in yeast; therefore, the text below will be defined as yeast if there is no extra interpretation.

2. Chromatin remodeler

As we know, the position and status of chromatin structure are not permanently stable; conversely, it is dynamically regulated by chromatin remodeling complexes, by using the energy of ATP hydrolysis to create a force to promote the local repositioning of nucleosomes and alter the accessibility of DNA elements to transcription factors and (or) other proteins [16, 17]. The activity of the ATP-dependent chromatin remodelers includes the exchange of core histones/histone variants, the eviction of histones from nucleosomes, and the repositioning or sliding of nucleosomes along DNA [18–20].

All the ATP-dependent chromatin remodeling complexes are multi-subunit complexes containing an ATPase subunit of the Snf2 (sucrose non-fermenting 2)-type of helicase. Based on the structural characteristics of this catalytic ATPases subunit, the ATP-dependent chromatin-remodeling complexes can be classified into four subfamilies, including SWI/SNF (switch/sucrose non-fermentable), ISW1 (imitation switch), CHD (chromodomain-helicase DNA-binding protein), and INO80

(inositol requiring 80) (**Figure 1**) [21–27]. Currently, the most thoroughly studied remodelers are SWI/SNF subfamily [28, 29], which is defined by its N-terminal HSA (Helicase-SANT–associated) domain working for binding actin and other actin-related proteins [30]. The histone acetylated-lysine binding domain is located at C-terminal, named bromo domain [31]. This remodeler family is large, multi-subunit complex that contains more than eight proteins.

Here in **Table 1**, we summarized these four chromatin-remodeler families and their subunits, and other functional domains are also described.

The formation of nucleosome structure is the natural obstacle for the processes of DNA replication and transcription (*please keep in mind that nucleosome structure also protects the fragile DNA from insult). How does the cell work for transcription under the condition of chromatin? One of the mechanisms is histone exchange or removal from nucleosomes mediated by histone chaperon and/or chromatin remodeler. For example, when activated transcription occurs, chromatin remodelers such as the Remodels the Structure of Chromatin (RSC) complex maintain these nucleosome-depleted regions (NDRs) by sliding nucleosomes away from the promotor region, allowing the binding of RNA polymerase II to the promoter [32, 33]. In addition, chromatin remodeling complexes promote the binding of transcription activators on gene promoters or enhancers region, finally resulting in the gene activation. However, the formation of the NDR alone does not ensure Pol II-mediated transcription initiation on special gene locus. This indicates that other mechanisms may be involved in this process. For example, it is shown that histone variant H2A.Z is specially located on the two nucleosomes flanking the NDR (denoted as −1 and +1 with respect to the NDR) at certain genes, promoting or inhibiting gene expression. The incorporation and removal of H2A.Z into +1 and −1 nucleosomes are mediated by chromatin remodeling complex SWR and INO80 [34, 35].

Both the processes of DNA replication and RNA transcription involve nucleosome assembly and organization, the histone complexes (H3–H4 tetramers and H2A–H2B dimers) are delivered by histone chaperones for chromatin-remodeler (including ISWI and CHD subfamily). After DNA is exposed from histones, access subunit(s)

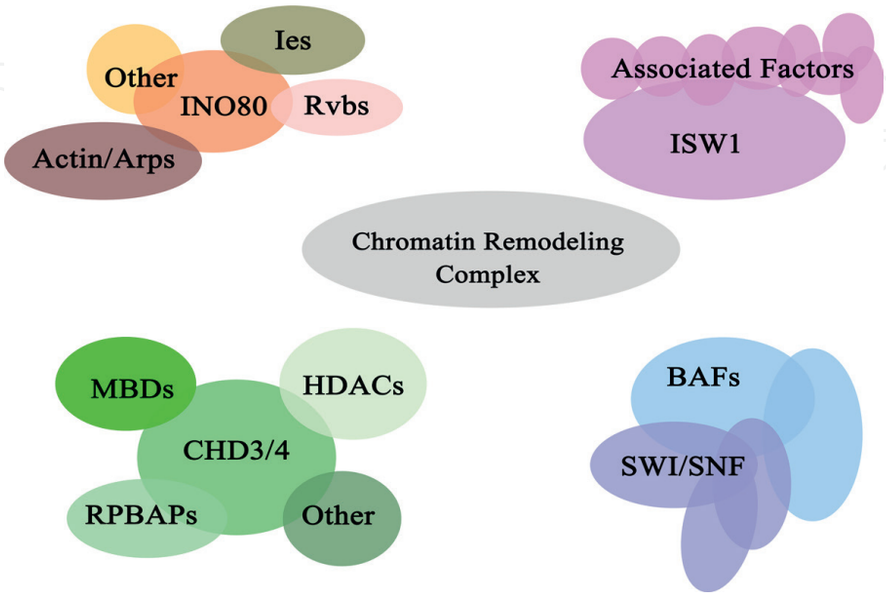

Figure 1.
Composition of the chromatin remodeler complexes.

Chromatin-remodeler families	Subunits	Domains	Functions
SWI/SNF	SWI1, SNF11, Swp82, SWI2/SNF2, Swp73, SWI3, Arp9, SNF5, Arp7, SNF6, Swp29	HSA	Actin binding
		DExx	ATPase
		HELICc	ATPase
		BROMO	Acetylated lysine binding
ISWI	ISW1, P74, p110, p105, ACF, RSF, CERF, CHRAC, NURF, NoRC, WICH, b-WICH	DExx	ATPase
		HELICc	ATPase
		SANT	Histone binding
		SLIDE	Histone binding
CHD	CHD1, CHD2, CHD3, CHD4, CHD9, NuRD	CHROMO	Histone binding
		DExx	ATPase
		HELICc	ATPase
INO80	Arp8, Arp4, Taf14, Ies4, Actin, Ino80, RvB1/2, Ies3, Ies1, Ies2, Arp5, Nhp10, Ies5, Ies6, SRCAP	HSA	Actin binding
		DExx	ATPase
		HELICc	ATPase

Table 1.
Four chromatin-remodeler families, subunits, and their respective functional domains.

of the remodelers will direct the binding of transcription activators or repressors on gene promoters or enhancers region. Meanwhile, remodelers also help to protect the "naked" DNA by recruiting other protein complexes, including the histone modification, transcription activator, or repressor complex, and during this process, the electrostatic environment and space surrounding the chromatin are also involved.

In addition, the nucleosome structure can be remodeled by the interaction between histones (variants) modifications and special recognizing subunits of the chromatin remodeler. The remodeler-specific domains recognizing and binding histone modifications, generally reference as reader domains. It is shown that the remodelers have a greater affinity for the nucleosome than naked DNA, which means the recognizing subunits have a priority to bind the modified histones [16]. For example, the PHD (plant homeodomain) finger domain, discovered over a decade ago in the Arabidopsis protein HAT3.1, is found in many chromatin-remodeling proteins. It functions as an "effector" that can recognize histone H3 tail peptides at lysine 4 (H3K4me2 and H3K4me3) [36–39], further recruiting transcription factors and nucleosome-associated complexes to chromatin. Bromo domain, another protein recognition module, recognizes and binds acetyl-lysine residues on histone tails protruding from the nucleosome [40, 41].

Meanwhile, the histone variants also influence the affinity of these remodeler subfamilies, and certain histone modification variants markers can recruit specific chromatin remodeling complexes and further reinforce the remodeling. During this process, the chromatin remodelers play an important role in the "position effect" of gene expression [42, 43]. There are also some other protein recognition modules that have been described in the past two decades; however, we will not describe them one by one here in this chapter.

3. Chromatin dynamics and histone modifications

Both histone tails and globular domains are subject to a vast array of different posttranslational modifications including acetylation, methylation, phosphorylation, deamination, β-N-acetylglucosamine, ADP ribosylation, (de)ubiquitylation, and SUMOylation [44]. Histone methylation frequently occurs at lysine (K) and arginine (R) residues, which is mediated by histone methyltransferase such as SET-1 (H3K4me), SET-2 (H3K36me), and PRMT5 (H3R8, H4R3); histone acetylation occurred at lysine residues is mediated by acetyltransferase, such as GCN5 (H3K9, K14, and K18) and HAT1 (H4K5 and K12). Phosphorylation occurred at serine and threonine residues is achieved by MSK1/2 (H3S28). Ubiquitination occurred at lysine residues is mediated by ubiquitinase such as RNF20/RNF40 (H2B120K). Histone modifications that are associated with active transcription are commonly referred to as euchromatin modifications, such as acetylation of histone 3 and histone 4 (H3 and H4) or di- or trimethylation of H3K4 [18, 44]. However, histone modifications that are occurred at inactive genes or regions are often termed heterochromatin modifications, such as H3K9me and H3K27me. There are two well characterized mechanisms for the function of histone modifications. The first is the disruption of contacts between nucleosomes and nucleosomes or DNA in order to "unravel" chromatin; the second is the recruitment of nonhistone proteins to bind to chromatin or to help remove histone/histone variant from chromatin [18]. Given the diversity of covalent modifications, it has been proposed that individual histone modifications or modification patterns might be read by other proteins that influence chromatin dynamics and function.

Many histone-modifying enzymes are components of chromatin remodeler complexes. For example, the Bdf1 subunit of chromatin remodeling complex SWR contains two bromodomains that bind to acetylated-lysine in H3 and H4 [45]. This indicates that the various kind of histone modifications cooperate with chromatin remodelers to modulate gene expression by altering the chromatin structure. From a genome-wide of view, histone H3K4me3 and H3ac are strongly correlated with active transcriptional start sites [46, 47]. Conversely, H3K9me3 are usually located on CpG island and mediates heterochromatin formation and gene silencing [48, 49].

In most cases, the chromatin-associated factors have been shown to specifically interact with modified histones rather than DNA, then chromatin remodelers are recruited to DNA locus independently. For the recruitment of chromatin remodeler

Chromatin remodeler readers/domains	Histone target(s)	Example
Bromodomain	Acetylation Lysine	H3K14ac [50]
Chromo domain	Methylation Lysine	H3K4me, H3K9me, H3K27me, H3K36me [51]
PWWP (Pro-Trp-Trp-Pro motif)	Methylation Lysine	H3K36me [52]
PHD finger	Methylation Lysine	H3K4me [53, 54]
MBT (malignant brain tumor) repeat	Methylation Lysine	H4K20me [55]
SANT domain	non-modified histone tails	[56, 57]

Table 2.
The major chromatin remodeler readers/domains and their binding histone targets.

complexes to chromatin, the transcription factors with distinct DNA binding domains work to direct the target selectivity and functional specificity.

Here, we summarize the chromatin remodeler readers and their histone targets with various modifications (**Table 2**).

In fact, all the epigenetic modifications cooperate with each other to guarantee an accurate regulation of gene expression. Certain histone modification markers can recruit specific chromatin remodeling complexes and further reinforce the remodeling of nucleosomes. During this process, the chromatin remodelers play an important role in the "position effect" of gene expression [16].

4. Crosstalk among chromatin dynamics, epigenetic modifications, and gene regulation

How to determine a gene's expression status? What extent should it be silenced or activated? The answer may depend on the chromatin position or the state of the target gene. Generally, each type of epigenetic modifications is dynamic and keeps on changing within the cell, and it is driven by cell signals induced by alterations in the cellular environment, including changes in nutrients, stress, hormone levels, and cell damage, etc. The cross-talk among chromatin dynamics, epigenetic modification, and gene expression regulation is an extra complex process via multiple possible mechanisms: (1) these events may be dependent on another; (2) they may work competitive; and (3) one factor disruption/mutation do not necessarily have

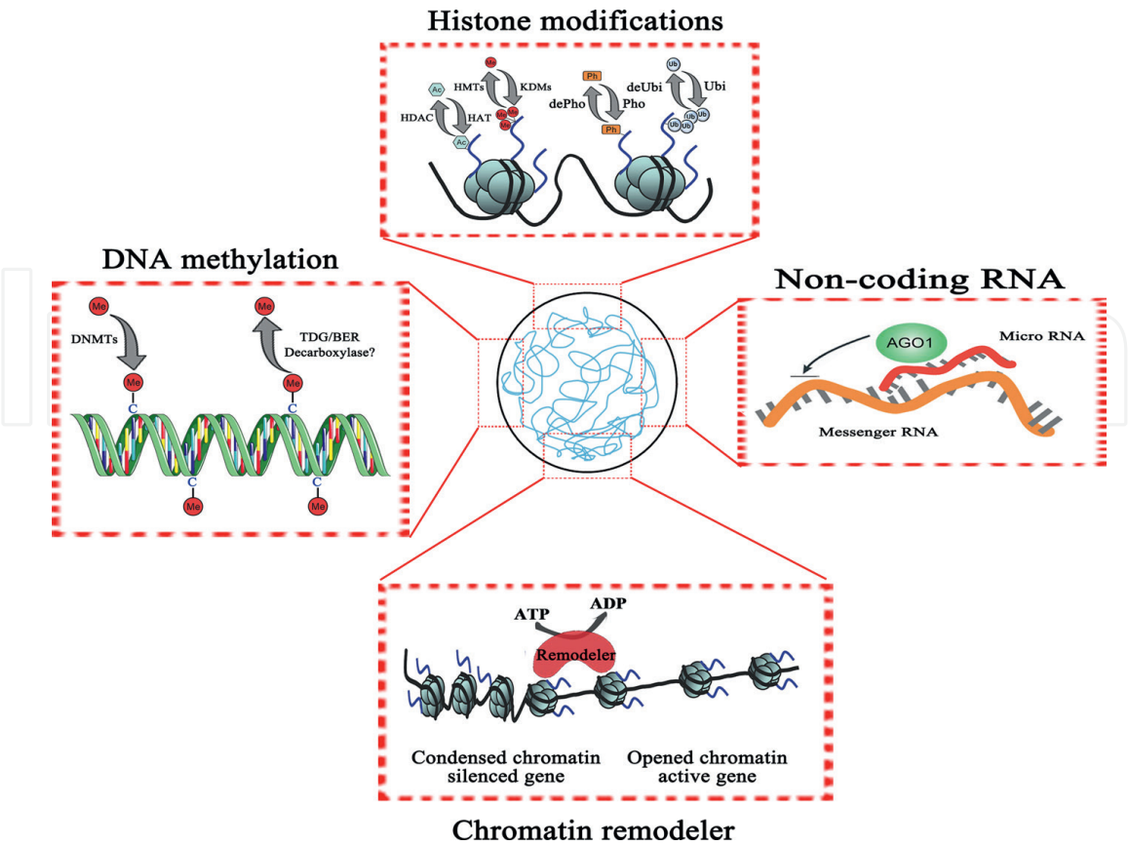

Figure 2.
Dynamic of epigenetic modifications.

effect on another directly. In addition, most of the genes, especially those involved in cell differentiation and proliferation, may have various layers of regulatory mechanisms [58]. For example, DNA methylation can reinforce histone modifications and strengthen chromatin structure, to ultimately activate or silence the expression of specific genes [59]. In some cases, they may function in competition to "check" each other to maintain homeostasis [60, 61]. A promotive histone modification marker and a repressive chromatin structure can co-exist to either keep gene expression at a moderate level or switch it "on and off" at different time points, quickly and efficiently [62, 63] (**Figure 2**). The histone modifications can direct the gene expression regulation by the chromatin remodeler. It was reported that H3K56Ac alters the substrate specificity of SWR-C, resulting the random switch of either H2A.Z/H2B with free H2A/H2B dimers from nucleosomes [64, 65]. Yeast INO80-mediated genome-wide distribution of H2A.Z facilitates DNA repair, transcription, and replication [65, 66]. On the other hand, the DNA sequence-directed transcriptional activators interact with chromatin remodelers and affect their activities. For example, the interaction between yeast SWI/SNF and a DNA-bound activator can promote nucleosome eviction in vitro [67–69].

5. Aberrant chromatin dynamics and disease

To remain healthy status, our bodies must maintain homeostasis by adjusting the expression levels of genes to resist the detrimental effect from the stimuli of the biological environment both inside and outside of the body. Epigenetic modifications could regulate the expression level of corresponding gene(s), ultimately achieving homeostasis.

Chromatin dynamics play a central role in regulating various key biological phenomena. Recently, it was reported that various mutations occur in these chromatin-remodeling families, resulting in the chromatin dysregulation and aberrant expression of target genes, and ultimately lead to various disorders. Chromatin dysregulation by abnormal remodelers is often linked to neurodevelopmental disorders [70–72] and intellectual disabilities [73, 74], and also result in immunodeficiency [75] and muscle wasting syndromes [76], and various cancers [22, 77–80].

Although the pathology is beyond the scope of this chapter, to illustrate some of these possibilities, we only take the cancer, CNS disorder, and aging as examples to highlight the chromatin dysfunction mechanisms below.

5.1 Cancer

Most of the published genome-wide chromatin modification studies indicate that malignant metamorphosis of cells is governed to a large degree by the fluctuating cellular environment. Chromatin remodelers work as gatekeepers to control the accessibility of DNA binding transcription factors and ensure the variety of biological functions within the cell. Crudely speaking, the tumorigenesis can occur via at least two mechanisms: (i) altering gene expression, and (ii) fragile genome integrity and/or chromosome segregation. Thus, any aberration on chromatin remodeling complexes has been linked with genome instability. Chromosome segregation defects are related with the malignant transformation and progression of tumors. Loss-of-function SWI/SNF subunit mutations are detected in most prevalent in various cancers. It is shown that ~20% of all human cancers contain mutations on subunits

of the SWI/SNF complex. The mutation of SWI/SNF subunit occur in ovarian clear cell carcinoma (75%), clear cell renal cell carcinoma (57%), hepatocellular carcinoma (40%), gastric cancer (36%), melanoma (34%), and pancreatic cancer (26%) [81, 82]. Among these ATP-dependent chromatin remodelers, SWI/SNF complex was first implicated in oncogenesis due to the discovery that its subunit SMARCB1 (also known as SNF5 and BAF47) is inactivated by biallelic mutations in nearly all cases of rhabdoid tumor [83]. Subsequently, accumulating researches reported that other subunits of SWI/SNF are mutated in various cancer types even though the mutated frequency is different in specific cancer type. For example, ARID1A is the most frequently mutated SWI/SNF subunit across cancer types [84, 85]; however, PBRM1 subunit mutations are much more common than ARID1A mutations in clear cell renal cell carcinoma [86]. Unlike the well-known role of SWI/SNF in cancers, the involvement of the other three subfamilies in cancer has not been well characterized. However, recent researches showed that all of the four chromatin remodeler subfamilies are implicated in pancreatic cancer (PDAC) by either mutation and/or chromosomal alterations [87]. Collectively, chromatin remodeling complexes is a potential target for therapeutic drugs design in the future.

Besides the point mutation or chromatin depletion, lots of mutations in epigenetic modifications occur in cancer cells compared to the normal healthy cell, which are epigenetic trademarks in earlier cancer development [88, 89]. With the abnormal epigenetic modifications, the cancer cells can maintain a portrait of self-renewal and unlimited proliferation. It has been found that cancer cells are usually marked with a loss of active H3K4me3 as well as repressive H4K20me3 and a gain of the repressive mark H3K9me3 or K3K27me3 [90, 91]. No matter altered gene expression or the instability of genome integrity during the process of tumorigenesis, questions then arise as to how do these aberrations changed the chromatin opening status and further influence the corresponding gene expression? Can we find out some methods like DNMT (DNA methyltransferases) inhibitor, HDAC (histone deacetylases) inhibitor, kinase inhibitors, etc., to reduce the detrimental effect? Or it is also worthy to modulate the balance between maturation and correction, thus favoring a status of recovery. Here, we did not expand into details and just attempt to take a short of paragraph on the chromatin dysfunction as well as some prospective pipelines for the fight against cancers.

5.2 CNS disorder

In the central nervous system (CNS) disease, epigenetic mechanisms serve as key regulators of development, homeostasis, and plasticity, all of which are highly sensitive to local and more global environmental, vascular, systemic, and intrinsic CNS factors [92, 93]. Not surprisingly, epigenetic modifications are involved in the molecular and cellular mechanisms underlying CNS pathogenesis and recovery, including the adult neurogenesis, response of initiate immunology, and neural plasticity. Disruption in the status of chromatin dynamics can lead to the changes in the site and the number of gene dysfunction. Thus, the gene regulation in chromatin level has an important role in the development of brain development. Abnormal chromatin is a key feature of necrotic cell death and apoptotic cell death, which are both associated with neural injury like stroke [94].

A growing body of evidence suggests that chromatin remodeling complexes that play a key role in vascular biology are involved in defining and transducing cardiovascular disease inheritability. The role of chromatin remodeling complexes in the transcriptional unit of protein-coding genes, especially the role of intragenic

chromatin modifications, is underappreciated and not well characterized in the current era of genome-wide studies. The role of chromatin remodelers in CNS development and recovery is multifaceted. It is involved in the vulnerability of the brain cells to injury, the sensitivity of neurons to inflammation stimuli, and the immune system recovery ability after injury. Currently, epigenetic modifications mechanisms have been applied in preclinical and clinical trials due to its critical roles in the regulation of immune responses process. It also become a potential therapeutic method for risk, onset, and progression of CNS disease. The initiate immunology within brain implicated in sophisticated cognitive functions, including neuronal-glial differentiation, the modulation of neural behavior and in higher brain functions like cognition, learning, and memory. It is worth noting that epigenetic mechanisms are involved in brain immune system development, homeostasis, and plasticity.

Importantly, it has been shown the practical application of epigenetics in cardiovascular disease therapeutics [94–96]. There is increasing interest in the role of chromatin remodelers in disease pathobiology, especially about whether and how pharmacological manipulation of epigenetic processes may allow for ischemic neuroprotection [97, 98]. It is possible that epigenetic modification may serve as a sensitive and specific biomarker to predict the CNS disease progression. Furthermore, several epigenetic agents are currently being evaluated in some fields such as neural cell survival and brain tissue repair and functional reorganization. Therefore, epigenetic mechanisms have been served as key regulators for mediating neuron development, homeostasis, and plasticity.

5.3 Aging

Aging is a major risk factor for many of the most prevalent diseases all over the world [99, 100]. Epigenetic dysregulation may contribute to aging in mammals [101]. An obvious correlation between aging and DNA methylation was observed in various mouse tissues. It was reported that the genes (EDARADD, TOM1L1, and NPTX2) responsible for aging are usually hypermethylated in the promoter CpG islands [102, 103].

As we all known, at the earlier development stage of the embryonic stem cells (ESCs) occupy a global "open" and dynamic chromatin state. When the cell differentiation is on the way to be mature, the chromatin configuration will transit from "open state" to a more compact and repressive state, which correlates with less dynamic exchange of chromatin proteins [104, 105]. There are clear changes to both the global and specific histone mark patterns with organisms increasing aging. For example, H3K9me3 is a hallmark of heterochromatin, and it is globally reduced in fibroblasts from HGPS patients [106]. H4K20me3 is also a mark of heterochromatin and transcriptional repression, but it tends to increase in fibroblasts from HGPS patients with increasing aging [106]. In addition, H3K27me3 is altered in a variety of cell types and species during aging. For example, there are increased levels of H3K27me3 in brain tissue from the senescent accelerated mouse SAMP8 with increasing age [107]. A fundamental question about aging is how chromatin dynamics are passed to relatively less active through a couple of generation cell divisions.

6. Therapeutic value targeting chromatin modification

Over the past decade, rapid progress has been made in the field of epigenetics research with the development of powerful technologies such as high-resolution

microscopy and genome-wide next-generation gene sequencing [108–110]. It is also very promising to use epigenetic modification changes as a diagnostic tool before the related disease develops. Several drugs designed according to the epigenetic modification have been already approved by the US Food and Drug Administration [111, 112]. Currently, epigenetic therapy is successfully applied in clinics for the treatment of hematological malignancies, but little success has been achieved in the treatment of solid tumors. However, notwithstanding the role of epigenetic regulation in the pathophysiology is not well characterized, emerging evidence suggests that it is extremely important to provide the strategies of clinic therapeutics.

7. Future perspective

Given that the various mutations occurred at different chromatin modification enzymes in different human cancers and other diseases, the investigation of specific mechanisms underlying the mutation of chromatin modification enzymes in different cancers/diseases will pave the way toward new therapeutic strategies for a range of human cancers with significant unmet medical need. In addition, from the perspective of the canonical role of chromatin remodeling complex in chromatin regulation [27], the following aspects will be the goals to develop the novel therapeutic drugs for parents with aberrant chromatin dysregulation by targeting the chromatin regulator or its associated protein. (1) designing the small molecular inhibitor against the chromatin regulators such as some specific subunits of SWI/SNF chromatin remodeling complex base on the fact that the subunits of mSWI/SNF (ARID1A, PBRM1, SMARCA4, and ARID2) are frequently mutated in many common human cancers, such as ovarian, colon, kidney, lung, prostate, breast, and others [113]; (2) designing the novel drugs targeting the transcription factor interacting with mutated chromatin remodeling complex is a potential alternative strategy to inhibit a variety of tumors driven by the interaction between oncogenic transcription factors and mutated chromatin remodeling complex; (3) given the critical role of chromatin remodeling complex in DNA replication and damage repair, it is also a potential therapeutic strategy to therapy the parents with tumor driven by aberrant chromatin regulator by targeting the replication- or repair-associated factors interacting with chromatin regulators. With increasing genetic, biochemical, and physiological understanding of chromatin remodeling complexes, their links to human diseases will continue to expand, providing new therapeutic opportunities across multiple disease areas. Given the fundamental role of chromatin regulators in normal physiology, future therapeutic approaches should focus on identifying the specific regulatory mechanisms of chromatin regulators in specific cancers/diseases to enhance overall therapeutic benefits.

8. Conclusion

Chromatin regulators are involved in priming transcriptional responses, and many chromatin modifiers and remodelers have been implicated in various human diseases. However, some chromatin alterations are potentially plastic and reversible, which raises the possibility of correcting chromatin states as a therapeutic strategy.

Probably the major debate is the association and order among gene expression, histone modification, and chromatin remodeler/dynamics, and it seemed impossible

to control only one factor and hence detect the target mechanisms selectively. Further, open question reminds what is the perfect feature of these factors to guarantee a so-called healthy condition?

Despite these contentions, the progress that made by the researchers have move forward to the intrinsically epigenetic regulators with the high-throughout gene sequencing and screening technology, the scientific data supplied from various database till date will form the ladder for the future therapeutic options.

Nevertheless, studies of epigenetics are increasing, and epigenetic therapies have become exciting and promising. The rise of new technologies such as CRISPR/Cas9 gene editing and next-generation sequencing in recent years allows us to better understand the interplay among epigenetic changes, gene regulation, and human disease, and it will lead to development of new approaches for molecular diagnosis and treatments across the clinical spectrum.

The use of epigenetics as a major contributing factor in the development of normal and abnormal cells will open new sights for the advent of new therapeutic approaches.

Epigenetic therapy can be combined with the traditional therapies to provide certain treatments for reversal of the drug-resistant tumors. Also, with this therapeutic approach, the drug dosages can be reduced to eliminate the side effects of treatment and, consequently, the patient's healing problems and increase the patients' quality of life.

Author contributions

SQ had the initial idea for this article. GC and QD prepared table and drafted the manuscript. SQ and KG performed the literature search and revise support. All authors critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Abbreviation list

Snf2	Sucrose non-fermenting 2.
SWI/SNF	Switch/sucrose non-fermentable.
ISW1	Imitation switch.
CHD	Chromodomain-helicase DNA-binding protein.
INO80	Inositol requiring 80.

HAS	Helicase-SANT–associated.
RSC	Remodels the Structure of Chromatin.
NDR	Nucleosome-depleted region.
PHD	Plant homeodomain.
PWWP	Pro-Trp-Trp-Pro motif.
MBT	Malignant brain tumor.
PDAC	Pancreatic cancer.
PTMs	Histone post-translational modifications.
DNMT	DNA methyltransferases.
HDAC	Histone deacetylases.
CNS	central nervous system.
ESCs	Embryonic stem cells.

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