Chapter 16
Therapeutic Significance of Chromatin Remodeling Complexes in Cancer

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Abstract The compaction of genomic DNA into chromatin has far-ranging consequences for almost all aspects of DNA metabolism activity. ATP-dependent chromatin remodeling complexes (CRCs) enable DNA-binding proteins access to nucelosomal DNA by altering chromatin structure through distinct mechanisms including nucleosome sliding, nucleosome assembly, and histone exchanges, in an energy-dependent manner. Consequently, CRCs play critical roles in diverse cellular processes that are dependent on chromatin template, including transcription, replication, and DNA repair. Thus, an aberration in these chromatin remodeling proteins leads to human diseases including cancer. In this chapter, we discuss the functional roles of CRCs in the regulation of gene transcription, DNA damage response, and its potential connection with cancer development as well as tumor therapeutics.

Keywords Chromatin remodeling • Transcription • DNA damage response • Cancer • Cancer development and progression • Cancer therapeutics

16.1 Introduction

It is increasingly accepted that cancer is a genetic disease. A precise understanding of how genetic alternations contribute to tumor development and progression is the key to develop effective strategies for winning the fight against cancer. The genetic

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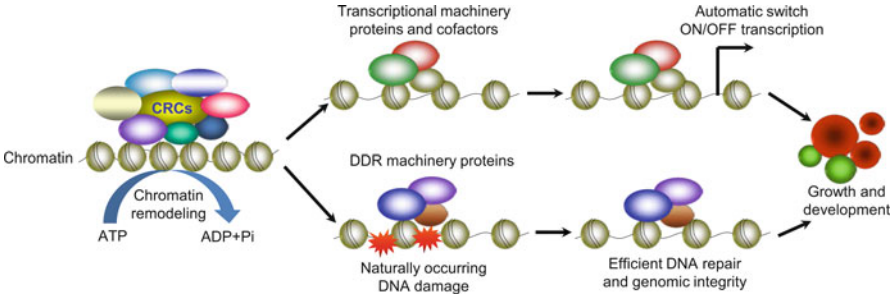

Fig. 16.1 Functional role of the CRCs in transcription and DDR. The CRCs alter chromatin structure in an energy-dependent manner. Consequently, the transcriptional and DDR machinery proteins get access to nucleosomal DNA and facilitate gene transcription and efficient DNA repair

material is stored into the nucleus in the form of chromatin. The fundamental building block of chromatin is the nucleosome core particle, which is made of approximately 147 base pairs of DNA wrapped around a histone octamer consisting of two copies of each of the four core histones H2A, H2B, H3, and H4 [1, 2]. The repeating nucleosome cores are connected by 20–80 base pairs of linker DNA and further assembled into hierarchically folded higher-order structures with the linker histone H1, nonhistone proteins and divalent metal ions [1–3]. By its very nature, the highly condensed structure of chromatin generally limits the accessibility of DNA binding proteins to the DNA, thus exerting an inhibitory effect on many critical DNA metabolizing activities, such as transcription, DNA replication, recombination and repair. To counteract this repressive barrier imposed by nucleosome architecture, eukaryotes have developed multiple intricate mechanisms to remodel nucleosomes, thus allowing DNA binding proteins such as transcription factors and DNA repair proteins access to the DNA. One of such mechanisms is involved in the ATP-dependent chromatin remodeling complexes (CRCs) that hydrolyze ATP to alter histone-DNA contacts through several mechanisms including nucleosome sliding, histone exchange, and nucleosome/histone eviction [4]. To date, four families of CRCs have been characterized in eukaryotes based on their compositions and functional domains, including the SWI/SNF (switching/sucrose non-fermenting), ISWI (imitation switch), Mi-2/NuRD (nucleosome remodeling and histone deacetylase), and INO80 (inositol requiring) [5, 6]. All CRCs are multisubunit complexes that contain an ATPase subunit [6] and most of them are conserved from yeast to humans. These CRCs play essential roles in many basic biological processes, including gene expression, DNA damage repair, and cell division (Fig. 16.1) [6–11]. Consequently, aberrations in these chromatin remodeling proteins are associated with a variety of human diseases including cancer. Thus, targeting the components of chromatin remodeling signaling pathways is currently being evaluated as a major therapeutic strategy in the prevention and treatment of human cancers. In the following sections, we focus on discussing the emerging role of CRCs in gene transcription, DNA damage response (DDR), and tumor development as well as its potential implication in cancer therapeutics.

16.2 Characterization of the CRC Family

The first discovered CRC family is the SWI/SNF, which was initially identified in independent screens for mutants affecting mating-type switching and growth on sucrose in 1994 [12–14]. The SWI/SNF family is composed of 8–14 subunits and is characterized by a bromodomain in its ATPase catalytic subunits, BRG1 (also known as SMARCA4 or BAF190A) and BRM (also known as SMARCA2 or BAF190B) http://www.genecards.org/ [15]. The bromodomain preferentially interacts with acetylated histones, which play both positive and negative roles in regulating the activity of the SWI/SNF remodeling factors [16]. In *S. cerevisiae*, this family contains the founding member SWI/SNF complex as well as the highly related RSC (remodel the structure of chromatin) complex [17]. Both SWI/SNF and RSC complexes exhibit a DNA-dependent ATPase activity to perturb nucleosome structure [17, 18], and contain nuclear actin-related proteins Arp7 and Arp9 [19, 20]. Arp7 and Arp9 form a stable heterodimer relying on their actin-related regions for heterodimerization, and function with DNA binding proteins to facilitate proper chromatin architecture and complex-complex interactions [19, 20]. Human complexes of this family have also been identified, including the BRG1-associated factor (BAF) complex and the polybromo BRG1-assocaited factor (PBAF) complex [21, 22]. With regard to homology, BAF1 is similar to the yeast SWI/SNF and PBAF is more like yeast RSC complex [21, 22].

The second family of CRCs is ISWI. One distinguishing feature of this family is that its ATPase subunit contains a carboxyl-terminal SANT and a SLIDE (SANT-like ISWI domain) domain, which together form a nucleosome recognition module that binds histone tails and linker DNA [23, 24]. The founding member of this family is the *Drosophila* NURF (nucleosome remodeling factor) complex, which was identified in 1995 by assaying the ability of drosophila embryo extracts to generate a nuclease-hypersensitive site within an array of nucleosomes [25]. NURF is composed of four distinct subunits, including the 140-kD ISWI ATPase subunit (NURF140) [26], a 55-kD WD repeat protein (NURF55) [27], the smallest NURF38 component [28], and the large NURF301 subunit [29]. In contrast to the SWI/SNF complex, the ATPase activity of NURF requires nucleosomes rather than free DNA or histones [25]. Thus, NURF acts directly on a nucleosome to alter chromatin structure by catalyzing nucleosome sliding, thereby exposing DNA sequences associated with nucleosomes [25, 30, 31]. Interestingly, the N-terminal histone tails are functionally important for modulating nucleosome mobility and regulating ATP-dependent nucleosome sliding by NURF [30]. In addition to NURF, the *drosophila* ISWI complex also contains the CHRAC (chromatin remodeling and assembly complex) [32] and ACF (ATP-utilizing chromatin remodeling and assembly factor) complexes [33]. Both exhibit chromatin assembly and nucleosome sliding activity in an ATP-dependent mechanism [32, 33]. In mammals, two highly related ATPase subunits of the ISWI CRC have been identified, including SNF2L (SNF2 like) and SNF2H (SNF2 homologue) [34]. Biochemical analysis revealed that the SNF2H ATPase catalytic subunit is contained in multiple complexes including ACF, CHRAC, RSF (remodeling and spacing factor), NoRC (nucleosome-remodeling complex), WICH (WSTF-ISWI chromatin remodeling), and WCRF (WSTF-related

chromatin-remodeling factor) [34–41]. In contrast, only a small number of complexes, such as the human NURF and CERF (CECR2-containing remodeling factor) complexes, contain the SNF2L ATPase subunit [35, 42].

The third family of CRCs is the Mi-2/NuRD complex, which was identified in1998 from several independent groups and processes both ATP-dependent chromatin remodeling and histone deacetylase activities [43–46]. The complex contains the histone deacetylases HDAC1/2, the histone-binding proteins RbAp46/48, the dermatomyositis-specific autoantigen Mi-2, the metastasis-associated proteins MTA1/2/3, and the methyl-CpG-binding domain proteins MBD2/3 [43, 44, 47]. Notably, Mi-2 subunit contains a chromodomain and plant homeo domain (PHD)-type zinc finger, and functions as a DNA-dependent, nucleosome-stimulated ATPase that remodels nucleosomes in an ATP-dependent manner [48]. In particular, Mi-2 lacking its chromodomains fails to bind or remodel nucleosomes [23].

The fourth family of CRCs is the evolutionarily conserved INO80 subfamily, which includes the INO80 complex and SWR1 complex [49]. The subfamily is characterized by a split ATPase domain and the presence of two RuvB-like proteins Rvb1 and Rvb2 [49]. The INO80 complex was initially purified from *S. cerevisiae* in 2000, consisting of about 12 subunits including Arp4, Arp5, Arp8, actin, and the Rvb1 and Rvb2 helicase proteins, and displays nucleosome-stimulated ATPase activity and ATP-dependent chromatin remodeling activities [50]. Deletion of Arp5 in yeast strains impairs INO80 ATPase activity, DNA binding, and nucleosome mobilization [51]. Similarly, Arp8 forms a complex with nucleosomes via the H3 and H4 histones [51, 52] and is essential for activity of INO80. In this context, deletion of Arp8 results in loss of INO80 function with multiple effects on cellular processes such as double-strand break (DSB) repair and chromosome alignment [52–55]. In contrast, Rvbp1p/Rvb2p is required for the complete assembly of a functional INO80 complex and for recruiting Arp5p to the INO80 complex in an ATP dependent manner [56]. The highly-related SWR1 complex was identified from *S. cerevisiae* in 2004 [57] and its human counterparts, termed Snf2-related CREBBP activator protein (SRCAP) and p400, were also identified afterward [58, 59]. In *S. cerevisiae*, this SWR1 complex contains Swr1p, a putative Swi2/Snf2-related ATPase, and 12 additional subunits. Among them, several subunits including Act1, Arp4, Rvb1 and Rvb2 are common to the INO80 complex [50]. Despite highly related to INO80, the SWR1 complex is unique in its ability to catalyze the incorporation of the histone variant H2AZ (Htz1 in *S. cerevisiae*) into nucleosomes [57, 60, 61], and this occurs in vitro in a stepwise and unidirectional fashion and requires dual activation with histone H2AZ and canonical nucleosome [62].

16.3 CRCs in Gene Transcription

The compaction of DNA into chromatin in the eukarytotic nucleus poses many obstacles to transcription [63]. The CRCs bind directly to nucleosomes and disrupt histone-DNA interactions using the energy of ATP hydrolysis, thus facilitating the access of the core transcription machinery proteins and general cofactors to nucleosomal DNA.

As a result, CRCs play a fundamental role in modulating transcription in yeast and higher eukaryotes. Notably, these CRCs have a range of specific and context-dependent roles in control of gene expression depending on the circumstance.

16.3.1 The SWI/SNF Complex

The SWI/SNF complex is involved in a variety of functionally distinct complexes and exerts diverse roles in gene regulation and genome function [64]. One outstanding example is that the SWI/SNF CRC participates in promoting transcriptional activation by nuclear receptors. The androgen receptor (AR) is a ligand-dependent transcription factor whose activity is tightly regulated by interacting cofactors and cofactor complexes and is a key player in prostate cancer development and progression [65, 66]. Considerable evidence has pointed out that the SWI/SNF CRC directs AR-mediated transcriptional activation, and different AR targets show disparity in the requirement for SWI/SNF [65–67]. A case in point is the BAF57 (also known as SMARCE1) subunit, which directly binds to the AR and is recruited to endogenous AR targets upon ligand activation, thus regulating AR activity, coactivator function, and AR-dependent proliferation [68]. Similarly, the BAF57 subunit specifically regulates estrogen receptor alpha (ERα)-dependent gene expression and proliferation in human breast cancer cells [69, 70]. Consequently, mutations in BAF57 deregulate several oncogenic signaling pathways, thus contributing to the development of breast cancer [71, 72].

In addition to BAF57, the BRG1subunit is a critical modulator of transcriptional regulation in various tissues and pathophysiological conditions [73]. For instance, BRG1predominantly interacts with Smad2 and Smad3 and is specifically required for transforming growth factor β-induced expression of endogenous Smad2/3 target genes through recruitment to Smad-dependent promoters [74, 75]. BRG1, as well as BRM, associates with the *CD44* and *E-cadherin* promoters and promotes their transcriptional activation in cancer cells through deceasing DNA methylation at their promoters [76]. In addition, SNF5 (also known as Ini1, BAF47, SNR1, or SMARCB1) mediates BRG1 recruitment to the $p15^{INK4b}$ and $p16^{INK4a}$ promoters and activates their expression through eviction of polycomb group silencing complex and extensive chromatin reprogramming [77].

Although the SWI/SNF CRC is generally associated with transcriptional activation, emerging evidence points out its additional role in transcriptional silencing pathway [78]. For instance, SWI3B, an essential subunit of the SWI/SNF complex, physically interacts with a long noncoding RNA (lncRNA)-binding protein, IDN2, and contributes to lncRNA-mediated transcriptional silencing [78]. Human BRM is functionally linked with the methyl-CpG binding protein MeCP2-depenendent transcriptional silencing [79]. Both BRG-1 and SNF5 subunits repress transcription of *cyclin D1* gene through the direct recruitment of histone deacetylase (HDAC) activity to its promoter, thereby exerting their tumor suppressor functions [80, 81]. More interestingly, BRG1 and BRM can switch their mode of function at same promoter between activation and repression through the context-dependent reprogramming of the SWI/SNF complex [82].

16.3.2 The ISWI Complex

The ISWI complex can space nucleosomes, thus affecting a variety of nuclear processes including transcription. Genome-wide analysis demonstrates that ISWI binds both genic and intergenic regions, and remarkably, binds genes near their promoters causing specific alterations in nucleosome positioning at the level of the transcription start sites [83]. Accumulating evidence suggests that the ISWI containing NURF complex is able to facilitate transcriptional activation via remodeling of chromatin in vitro and in vivo [29, 84, 85]. However, NURF also functions as a corepressor of a large set of JAK/STAT target genes in *drosophila* to regulate innate immunity network [86]. Similarly, ISWI and ACF1 directly repress Wingless transcriptional targets in *drosophila* [87]. In *S. cerevisiae*, Isw1 also functions in stress-induced gene repression under normal growth conditions [88]. In contrast, the Isw2 complex represses transcription of early meiotic genes during mitotic growth and this repressor function of lsw2 complex is largely dependent upon Ume6p, which recruits the complex to target genes [89, 90]. Subsequent studies further demonstrate that Isw2 acts as a transcriptional repressor by altering nucleosome positions, and loss of Isw2 activity results in the generation of both coding and noncoding transcripts due to inappropriate transcription [91].

16.3.3 The Mi-2/NuRD Complex

Accumulating evidence has uncovered a number of interesting connections between the Mi-2/NuRD complex and gene regulation [9, 92, 93]. A case in point is the metastasis-associated protein 1 (MTA1), the founding member of the MTA family, which was isolated by differential cDNA library screening using a rat mammary adenocarcinoma metastatic system [94]. MTA1 functions not only as a transcriptional repressor of estrogen receptor α [95], p21WAF1 [96], breast cancer type 1 susceptibility protein [97], RING finger protein 144A [98], phosphatase and tensin homolog [99], transforming growth factor β signaling component SMAD7 [100], guanine nucleotide-binding protein G(i) subunit alpha-2 [101], and homeobox protein SIX3 [102], but also as a transcriptional activator for certain genes, such as the breast cancer-amplified sequence 3 [103] paired box 5 [104], tumor suppressor alternative reading frame [105], cell surface oncogenic protein hyaluronan-mediated motility receptor [106], proto-oncogene protein Wnt-1 [107], and tyrosine hydroxylase [108]. One unanswered question in this field is what is the underlying mechanism for the physiologic switch between coactivator and corepressor functions of MTA1. It is becoming increasingly clear that post-translational modifications might play a role in the regulation of MTA1 function in transcription. In this context, SUMOylation and SUMO-interacting motif of MTA1 synergistically regulate its co-repressor activity on *PS2* transcription [109]. Similarly, acetylation status of MTA1 might also be crucial for its corepressor function on a negative modifier of

Ras activation and its oncogenic activity [101]. More interestingly, methylation of lysine 532 in MTA1 protein seemly represents a molecular switch between coactivator and corepressor [110]. In this context, methylated MTA1 is required for the NuRD repressor complex, while demethylated MTA1 recognizes the active histone mark and recruits coactivator complex onto its target gene promoters in a signaling-dependent manner [110].

16.3.4 The INO80 Complex

Involvement of the INO80 complex in transcription was first discovered in *S. cerevisiae*, in which INO80 facilitates transcription in vitro and in vivo [50, 111]. Subsequent studies further demonstrate that its mammalian orthologue also promotes transcription with transcription factor Yin-Yang-1 (YY1) [112]. In contrast, TBP-interacting protein 49b (TIP49b), a component of the INO80 complex, inhibits transcription factor 2 (ATF2) transcriptional activities in response to stress and DNA damage [113].

16.4 CCRs in the DDR

In response to DNA damage, chromatin undergoes a marked reorganization in an energy dependent manner, thus facilitating the DDR machinery proteins to recognize and repair the damaged DNA [114]. In addition to their putative roles in transcription, CCRs are intimately linked with the DDR.

16.4.1 The SWI/SNF Complex

The SWI/SNF complex is required for DNA replication [115, 116], somatic recombination [117], nucleotide excision repair (NER) [118, 119], and DSB repair [120]. SWI/SNF also regulates checkpoint activation after ultraviolet (UV) damage via regulation of the proliferating cell nuclear antigen-binding proteins Gadd45a and p21 [121]. The highly related RSC complex is also linked with efficient DSB repair [122, 123]. Interestingly, two isoforms of this complex, defined by the presence of either Rsc1 or Rsc2, play distinct roles in DDR and that at least part of the functional specificity is dictated by the bromo-adjacent homology (BAH) domains [124]. Moreover, the RSC and SWI/SNF chromatin remodelers play distinct roles in DSB repair; SWI/SNF is required during the early steps of homologous recombination (HR), while RSC is important upon the completion of the repair process [125].

16.4.2 The ISWI Complex

SNF2H, the catalytic subunit of ISWI complex, is rapidly recruited to DSBs in a poly(ADP-ribose) polymerase 1 (PARP1)-dependent manner and facilitates the RNF168-dependent signaling and repair of DSBs [126]. Similarly, the ACF1 chromatin remodeling factor accumulates at UV-induced DNA damage sites immediately following UV radiation [127] and promotes NER of UV-induced DNA lesions [128]. Similarly, the ACF1 complex accumulates rapidly at DSBs and is also required for non-homologous end joining (NHEJ) repair of DSBs in human cells [129]. Rsf-1 (also known as HBXAP) protein interacts with SNF2H to form an ISWI complex, RSF, and has been reported as an amplified gene in human cancers, including the highly aggressive ovarian serous carcinoma [130]. Emerging evidence shows that Rsf-1induces DNA damage and promotes genomic instability [131], and consequently, high-grade ovarian serous carcinomas, especially those with Rsf-1 overexpression, exhibit high levels of the DDR [132]. These findings highlight that increased Rsf-1 expression in tumors can induce chromosomal instability probably through DDR [131].

16.4.3 The Mi2/NuRD Complex

The initial link between the NuRD complex and DDR was found in 1999 [133], when Schmidt and colleagues discovered that ataxia telangiectasia and Rad3-related protein (ATR), a master regulator of the DDR, associates with multiple components of the NuRD complex, including MTA1, MTA2, HDAC1, HDAC2, and CHD4 [133]. Afterward, van Haaften G et al. in 2006 defined a role for *C. elegans* early growth response protein 1 (Egr-1), the homologue of human *MTA2* gene, in cellular sensitivity to ionizing radiation (IR) using a genome-wide RNA interference screening [134]. In 2009, Li et al. further discovered a previously unknown role for MTA1in IR-induced DSB repair and cell survival using MTA1-knockout fibroblasts [135]. In 2010, several studies from four different groups simultaneously reported a conserved role of the NuRD complex, including MTA1, MTA2, CHD4, HDAC1, and HDAC2 in DDR and DNA repair in multiple model systems [136–140].

The PARP family of proteins has been implicated in recruitment of proteins to sites of damage and is known to localize rapidly to sites of damage [136, 141]. In support of our early findings, emerging evidence shows that MTA1 is recruited to sites of DNA damage in a PARP-dependent manner, and depletion of MTA1 by siRNAs renders cells sensitive to IR, further highlighting its importance in promoting DNA repair [136]. The human homologue of *egr-1*, MTA2, also protects human cells against IR, suggesting its conserved role in the DDR [139]. CHD4 is rapidly recruited to DSBs in a PARP-dependent manner [136, 138], where it promotes RNF8/RNF168-mediated histone ubiquitylation and the ubiquitin-dependent accumulation of RNF168 and BRCA1 at sites of DNA lesions [137, 139]. CHD4 also

acts as an important regulator of the G1/S cell-cycle transition by controlling p53 deacetylation [138]. Consequently, loss of CHD4 causes defects in DNA repair and checkpoint activation, resulting in accumulation of spontaneous DNA damage and increased IR sensitivity [138, 139]. Furthermore, human HDAC1 and HDAC2 also function in the DDR to promote NHEJ repair [140]. Consistently, HDAC inhibitors block the activity of HDAC1 and HDAC2, resulting in defects in the DDR and hypersensitivity to the DSB-inducing agents [140]. Taken together, the NuRD chromatin–remodeling complex is a novel DDR factor that helps to preserve genome stability by regulating signaling and repair of DNA damage [11, 142]. Interestingly, recent studies pointed out that multiple NuRD components are lost during premature and normal ageing, resulting in accumulation of DNA damage during ageing [143], which could contribute to aging-related genomic instability and cancer [144].

16.4.4 The INO80 Complex

In addition to their well-established role in regulating transcriptional processes, accumulating evidence shows that INO80 and SWR1 chromatin remodeling components are essential for maintaining genomic integrity [10]. The INO80 complex is recruited to sites of DSBs through a specific interaction with the DNA damage-induced phosphorylated histone H2A (termed γH2AX) [145, 146], and mediates DSB repair through its role in DNA end strand resection [147]. INO80 is also recruited to sites of UV lesion repair through interactions with the NER apparatus and promotes the removal of UV lesions by the NER pathway [148, 149]. Moreover, INO80 is required for the restoration of chromatin structure after repair in response to UV-induced damage [149]. Interestingly, INO80 also shapes the DNA replication landscape. In this context, INO80 complexes are enriched at sites of replication and are required for efficient replication of late-replicating regions during replication stress through regulating S-phase checkpoint activity [4, 150]. INO80 also regulates the threshold of DNA damage during replication phase via modifying PCNA ubiquitination and Rad51-mediated processing of recombination intermediates at impeded replication forks [151–153].

16.5 CRCs in Cancer Development and Progression

16.5.1 The SWI/SNF Complex

Given its central function in epigenetic chromatin remodeling mechanisms, it is not surprising that alternation of the SWI/SNF CRC plays an important role in tumor development and progression. A substantial body of evidence indicates that several components of the SWI/SNF complexes function as tumor suppressors or negative

regulator of cellular proliferation [21, 154, 155]. One such example is the SNF5 core subunit, which has been documented to be mutated or inactivated in a number of human cancers including rhabdoid, rhabdomyosarcoma, epithelioid sarcoma, chronic myeloid leukemia, medulloblastomas, choroid plexus carcinomas, and melanoma [156–161]. In support of this notion, haploinsufficiency of SNF5 predisposes to malignant rhabdoid tumors in mice, and loss of SNF5 results in highly penetrant cancer predisposition with 100 % of mice developing T cell lymphoma or rhabdoid tumors with a median onset of only 11 weeks [162]. Collective evidence establishes that the tumor suppressor activity of SNF5 depends on its regulation of cell cycle progression, cell survival and senescence [163–168]. Inactivation of the SNF5 tumor suppressor stimulates cell cycle progression and cooperates with p53 loss to accelerate oncogenic transformation and tumor growth in mice [169, 170]. The inhibition of RhoA-dependent migration is another crucial tumor suppressor function of hSNF5, and its loss-of-function may lead to increased invasiveness and metastatic potential of cancer cells [171].

Another example is the ARID1A (also known as BAF250A, SMARCF1, p270, or hOSA1), which encodes a human homolog of yeast SWI1. The significance of ARID1A loss or mutation in cancer is now subject to intensive investigation. In this context, mutation of the *ARID1A* gene has been widely described in a broad array of tumor types, including gynecologic ovarian and endotrial carcinomas, pediatric Burkitt lymphoma, gastric carcinoma, breast cancer, and hepatitis B virus-associated hepatocellular carcinoma [172–178]. Consistently, restoring wild-type ARID1A expression in cancer cells that harbor ARID1A mutations is sufficient to suppress cell proliferation and tumor growth in mice [172, 175]. In contrast, ARID1A knockdown significantly promotes the proliferation, migration and invasion of cancer cells [173]. Functional evidence further points out that ARID1A collaborates with p53 to regulate p21WAF1 and SMAD family member 3 [179]. Together, accumulating genomic and functional evidence strongly supports classification of ARID1A as a tumor suppressor [177]. Similar to ARID1A, ARID1B (also known as BAF250B, or hOsa2) also inhibits cell growth and regulates cell cycle arrest through differentially regulating *c-myc* and *p21WAF1* gene expression [180].

In addition, loss or inactivation of BRG1, BRM, BAF155/SMARCC1, BAF180, and BAF200/ARID2 expression represents another mechanism for SWI/SNF complex in the development in human cancers, including hepatitis C infection-related liver cancer, melanoma, lung, pancreatic, skin, and breast cancers [21, 181–188]. Notably, BRG1 and BRM are silenced by different mechanisms. BRG1 is commonly silenced by loss-of-function mutations, whereas epigenetic silencing is a major mechanism for the loss of BRM in human cancer cells [188].

16.5.2 The ISWI Complex

A well-studied example is the Rsf-1, which plays an important role in cellular growth, survival, and oncogenic transformation, and its up-regulation is closely

associated with disease aggressiveness and poor prognosis in patients with various types of human cancers including bladder, colon, nasopharyngeal, gallbladder, oral, and ovarian carcinomas [130, 189–197]. A mechanistic study demonstrates that Rsf-1 interacts and collaborates with cyclin E1 in neoplastic transformation and p53 mutations are a prerequisite for tumour-promoting functions of the RSF/cyclin E1 complex [194]. In contrast, overexpression of Rsf-1 is rare in breast cancer, indicating that Rsf-1 is not a critical gene in breast cancer development [130, 198]. In contrast, SNF2L, a mammalian ISWI ortholog, suppresses cell proliferation and migration in human HeLa cells by attenuating Wnt signaling [199].

16.5.3 The Mi2/NuRD Complex

Of all the NuRD complex subunits, the MTA family members are best studied in the context of cancer development [92, 93]. MTA1, the founding member of the MTA1 family, has been documented to be overexpressed in a variety of human cancers and is significantly associated with tumor progression and poor clinical outcome [92, 93]. In contrast, the information concerning the expression of MTA2 and MTA3 in human cancers is limited. Like MTA1, increased expression of HDAC1 and HDAC2 has been documented in a variety of human cancers and linked with therapeutic resistance [200–202]. In contrast, lysine-specific demethylase 1, a newly identified component of the Mi-2/NuRD complex, inhibits the invasion of breast cancer cells in vitro and suppresses breast cancer metastatic potential in vivo [203].

16.5.4 The INO80 Complex

Although the function of the INO80 complex in transcription and DDR, its connection with human cancers is rarely reported. The SRCAP, a homolog of Swr1 in human cells, modulates expression of prostate specific antigen and cellular proliferation in prostate cancer cells [204]. Similarly, p400, another Swr1 homolog, inhibits p53-mediated *p21WAF1* transcription and the development of premature senescence [205]. P400 is an essential E1A transformation target that plays a major role in the E1A transforming process [206].

16.6 CRCs in Cancer Therapeutics

Glucocorticoids are used in the curative treatment of acute lymphoblastic leukemia (ALL) and resistance to glucocorticoids is an important adverse prognostic factor in newly diagnosed ALL patients [207]. Emerging evidence suggests that decreased expression of the BRG1, ARID1A, and SNF5 subunits appears to be associated

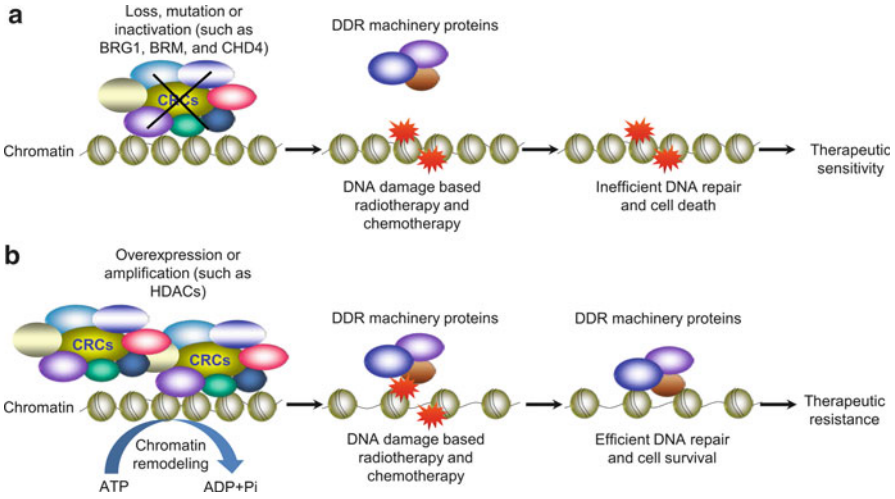

Fig. 16.2 Implication of CRCs in cancer therapeutics. Cancer cells with loss, mutation, or inactivation of the CRC components such as of BRG1, BRM and CHD4 are sensitive to DNA damage based radiotherapy and chemotherapy due to impaired DNA repair (**a**). In contrast, the CRC subunits such as HDACs are over expressed or amplified in cancer cells and promote efficient DNA repair, thus contributing to therapeutic resistance to DNA damage based radiotherapy and chemotherapy (**b**)

with glucocorticoid resistance in primary ALL cells [207]. Similarly, knockdown of BRG1 and BRM enhances cellular sensitivity to chemotherapy drug cisplatin by regulating efficient repair of the cisplatin DNA lesions [208]. Thus, cisplatin chemotherapy could be more effective in BRG1- and BRM-negative or inactivated tumors (Fig. 16.2a). Consistent with these findings, depletion of CHD4 renders cell significantly hypersensitive to DSB-inducing agents and PARP inhibitors as a consequence of impaired HR repair (Fig. 16.2a) [209]. As loss or mutation of BRG1, BRM and CHD4 has been observed in a variety of human cancers [186, 188, 210, 211], it is highly interesting to examine whether these tumors are sensitive to PAPR inhibitors or other DNA-damaging agents.

In contrast, overexpression of some components of CRCs is linked with therapeutic resistance (Fig. 16.2b). For instance, Rsf-1 overexpression confers paclitaxel resistance in ovarian cancer cells [212] and is associated with poor therapeutic response in rectal cancer patients treated with neoadjuvant chemoradiation therapy [191] and associated with incomplete response to radiotherapy in patients with nasopharyngeal carcinoma [192]. Notably, the Rsf-1-hSNF2H interaction is essential for developing resistance phenotype in tumors overexpressing Rsf-1 [212]. Thus, inhibition of Rsf-1 activity or disruption of the Rsf-1-hSNF2H interaction has the potential to sensitize cells to paclitaxel in human cancers with Rsf-1 amplication or overexpression. Similarly, HDAC2 is highly expressed in pancreatic ductal adenocarcinoma (PDAC) and confers resistance towards the topoisomerase II inhibitor etoposide in PDAC cells [201]. Consistently, selective inhibition of HDACs synergises with etoposide to induce apoptosis in PDAC cells [201]. In a broader

perspective, targeting the CRC-mediated DNA repair pathways might provide unique potential therapeutic avenues for human cancers when used in combination with DNA-damaging chemotherapeutic drugs [213, 214].

16.7 Conclusions and Perspectives

During the past decades, it has been made great progress in our understanding of the functional roles for ATP-dependent CRCs in transcription and DDR, and it has been increasingly recognized that these CRCs show remarkable diversity and specifity in their contributions to these biological processes. However, it remains unknown why the transcription and DDR pathways need multiple CCRs and whether or how these CRCs exert their functions in these processes in an integrated manner at molecular levels. In addition, the detailed mechanisms by which these CRCs regulate transcription and DDR and drive tumorigenesis and progression are largely unclear.

From a translational perspective, the importance of the CRCs in cancer causation and progression provides new avenues to improve cancer management by targeting the chromatin remodeling machinery. One example is that the CRCs predominantly function in the DNA repair pathways, which may contribute to therapeutic resistance in patients with cancers by enabling cancer cells to survival DNA damage induced by chemotherapeutic agents and radiotherapy [214]. Thus, targeting the CRC components and related DNA repair signaling pathways in human cancers could be efficacious as monotherapy or in combination with DNA-damaging agents [213, 214]. A case in point is the HDACs, whose inhibitors are emerging as promising drugs for cancer therapy that selectively kill cancer cells and sensitize cancer cells to DSB-inducing agents [200]. On the other hand, as components of the CRCs are frequently mutated in human cancers, this unique property of cancer cells gives a great opportunity to screen appropriate patients in clinic for optimum personal therapy using DNA-damaging radiotherapy and chemotherapy. Together, further work that directs to understand the in vivo function and mechanism of action of these CRCs will definitely provide opportunities to discover new therapeutic targets and therapeutic strategies for the treatment of cancer as well as other CRC-related diseases.

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