Epigenomic Regulation of Oncogenesis by Chromatin Remodeling

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ABSTRACT

Disruption of the intricate gene expression program represents one of major driving factors for the development, progression and maintenance of human cancer, and is often associated with acquired therapeutic resistance. At the molecular level, cancerous phenotypes are the outcome of cellular functions of critical genes, regulatory interactions of histones, and chromatin remodeling complexes in response to dynamic and persistent upstream signals. A large body of genetic and biochemical evidence suggests that the chromatin remodelers integrate the extracellular and cytoplasmic signals to control gene activity. Consequently, widespread dysregulation of chromatin remodelers and the resulting inappropriate expression of regulatory genes, together, lead to oncogenesis. We summarize the recent developments and current state of the dysregulation of the chromatin remodeling components as the driving mechanism underlying the growth and progression of human tumors. Because chromatin remodelers, modifying enzymes and protein-protein interactions participate in interpreting the epigenetic code, selective chromatin remodelers and bromodomains have emerged as new frontiers for pharmacological intervention to develop future anti-cancer strategies to be used either as single-agent or in combination therapies with chemotherapeutics or radiotherapy.

INTRODUCTION

Disruption of the intricate gene expression program in the context of chromatin is one of major driving factors for the development, progression and maintenance of human cancer, and often associated acquired therapeutic resistance. At the molecular level, cancerous phenotypes are the outcome of cellular functions of gene products - including underlying transcription and post-translational events, regulatory interactions of histone and non-histone proteins, and chromatin remodeling, in-general, in response to dynamic and persistent upstream signals. The building block of chromatin are nucleosomes -147 base pairs of DNA wrapped over an octamer unit which is composed of pairs of the histones H2A, H2B, H3, and H4.[1] Nucleosomes are further assembled to form higher-order chromatin with the linker histone H1, non-histone proteins and metal ions.[2] The highly organized chromatin structure constitutes a significant barrier for the eukaryotic transcription machinery gaining access only to small regions of DNA during gene transcription.[3]

The complexity of mechanisms regulating gene expression is steadily increasing and now comprises a complex interplay of factors mediated by chromatin topology, cross talk of post-translational modifications on histones and other nuclear proteins, modification of DNA itself and the architecture of gene promoters driven by cis acting elements such as enhancers and silencers as well as non-coding RNA sequences. Recent literature suggests that dysfunction of these regulatory elements results in alterations in gene transcription programs driving disease specific gene expression and thus, highlights the significance of transcription as a major mechanism for driving tumor growth and neoplastic transformation. Therefore, chromatin modifying enzymes and protein interactors that interpret the complex language of the epigenetic code have emerged as promising targets for cancer therapy. However, the complexity of mechanisms regulating gene transcription poses a significant challenge on the mode of action of developed drugs and tool molecules. Here we focus on the current state of target protein interactions present in chromatin remodeling enzymes

and nuclear scaffolding proteins and the underlying molecular mechanisms that govern the effects of these inhibitors on gene transcription in cancer.

CHROMATIN REMODELERS as INTEGRATORS of EXTRACELLULAR and CYTOPLASMIC SIGNALS into GENE ACTIVITY

To execute a timely and precise gene transcription response, eukaryotic cells employ multiple mechanisms to overcome the barrier created by densely packed nucleosomes. One such well-recognized mechanism involves the ATP-dependent chromatin remodeling complexes (remodelers), which utilize the energy derived from ATP hydrolysis to restructure nucleosomes to gain access to the target gene chromatin.[1, 4-6] There are, at least four families of well-characterized chromatin remodeling complexes in eukaryotes, including the switching defective/ sucrose non-fermenting (SWI/SNF),[7] the imitation-switch (ISWI) family,[8] the Mi-2/nucleosome remodeling and histone deacetylation (NuRD),[9] and the inositol 80 (INO80) family.[10] Each of these families (Figure 1) contains one or two distinct SWI2/SNF2-type catalytic ATPases and multiple associated subunits that contribute to a complex specificity in various biological contexts.[1, 6, 11]

A large body of genetic and biochemical evidence suggests that extracellular and cytoplasmic signals - such as growth factors, cytokines, hormones, metabolites - enable the eukaryotic transcription machinery to recruit the chromatin remodelers to the target gene chromatin, allowing expression through modulating DNA accessibility in a context-dependent manner.[12-15] Therefore, the chromatin remodelers act as an integrator of the extracellular and cytoplasmic signals to the nucleus for precise regulation of target gene expression. Consequently, disruption of chromatin remodelers is intimately implicated in cancer development, progression and therapeutic resistance due to dysregulation of the gene transcription program. Because of these essential functions, a

better insight into the chromatin remodeler machinery has surfaced as a new frontier for developing the next generation of anti-cancer therapeutic strategies.

CHROMATIN REMODELERS IN-ACTION

The SWI/SNF family: The SWI/SNF complex contains 12 to15 subunits, including the catalytic ATPase subunits (either BRG1 (SMARCA4) or BRM (SMARCA2)), several alternate core subunits (BAF250, BAF200), BAF47 (SMARCB1), BAF155 (SMARCC1), and BAF170 (SMARCC2), and other selected accessory subunits.[16, 17] Recently, the proteomic approach to the mammalian SWI/SNF complex has recognized a few new sub-components such as BCL7 and BCL11 isoforms, and the bromodomain protein BRD9 and BRD7.[18] Based on the subunit composition, the SWI/SNF complexes are generally grouped into two-types of complexes; BAF complexes containing ATPase BRG1 or BRM along with BAF250a (ARID1A) or BAF250b (ARID1B), while PBAF (polybromo-associated BAF) complexes only contains the BRG1 ATPase in addition to BAF180 (PBRM1) and BAF200 (ARID2) subunits[17, 19] (Figure 1B). The majority of SWI/SNF subunits are capable of directly binding to DNA or nucleosomes and disrupting histone-DNA interactions and thus, modulate the transcription of the target genes.[20, 21] In addition, the SWI/SNF chromatin remodelers also regulate the activity of non-chromatin substrates, such as the checkpoint kinase Mec1 (ATR in mammals) during cell-cycle progression.[22]

The ISWI family: The ATPase subunit of the ISWI chromatin remodelers was first discovered in *Drosophila,*[23] which forms the catalytic core of three distinct protein complexes, including nucleosome remodeling factor NURF,[23, 24] ATP-utilizing chromatin assembly and remodeling factor ACF,[25] and chromatin accessibility complex CHRAC.[26] In contrast, human ISWI chromatin remodelers have two ISWI ATPase subunits, hSNF2H (SMARCA5) and hSNF2L (SMARCA1),[27]

[28]. Biochemically, SNF2H is the ATPase catalytic core subunit of multiple ISWI chromatin remodeling complexes in humans, such as hACF,[29] hCHRAC,[30] and RSF (remodeling and spacing factor),[31] while hSNF2L forms the human NURF complex[32] (Figure 1B). The catalytic subunit ISWI drives nucleosome assembly or changes nucleosome structure,[33] and the HAND-SANT-SLIDE domain of the ISWI catalytic subunit is required for its remodeling activity.[34, 35]

Drosophila NURF, the first recognized remodeling factor belong to the ISWI family and is composed of four distinct subunits, including the ISWI ATPase NURF140[23] - the largest subunit NURF301,[36] the inorganic pyrophosphatase NURF38,[37] and the 55-kD WD repeat protein NURF55.[38] From the functional point of view, the NURF140 and NURF301 subunits are important for nucleosome sliding.[36] In contrast, NURF55 facilitates the formation of protein complexes with roles in chromatin metabolism,[38] while NURF38 may have a structural or regulatory role in the multi-protein complexes.[37] In humans, the NURF complex consists of SNF2L, BPTF (Bromodomain and PHD finger-containing transcription factor), and retinoblastoma-associated proteins RbAP46/RbAP48.[32] Drosophila ACF remodeler contains the Acf1 and ISWI subunits and promotes chromatin assembly and nucleosome remodeling during transcriptional activation.[25, 39] Human ACF is comprised of SNF2H and Acf1, and gauges the length of DNA with the help of histone H4 tail.[40] CHRAC in Drosophila contains at least five subunits, including the ATPase ISWI and topoisomerase II,[26] the largest subunit Acf1,[41] and two developmentally regulated components CHRAC14 and CHRAC16.[42] The human CHRAC complex contains hACF1 and p17 and p15 with roles in histone folding, but does not contain topoisomerase II.[30] In addition, human RSF is composed of the nucleosome-dependent ATPase hSNF2H and the histone chaperone Rsf-1, and possesses chromatin remodeling and chromatin assembly activities.[31, 43] Multiple lines of experimental evidence have demonstrated that the above-mentioned ISWI chromatin remodelers

play a key role in regulating gene transcription and genomic stability in the context of chromatin.[44, 45]

The Mi-2/NuRD family: The Mi-2/NuRD complex possesses histone deacetylation as well as ATP-dependent nucleosome remodeling activities.[46-49] The Mi-2/NuRD complex consists of the catalytic subunits CHD3 and CHD4, diverse HDACs, RbAp48 and RbAp46 with roles in histone binding, the metastasis-associated protein family proteins MTA1-3, and the methyl-CpG-binding domain family proteins MBD2 and MBD3[46-50] (Figure 1B). Among the NuRD complex, the CHD3 and CHD4 proteins contain a catalytic ATPase module and are involved in chromatin assembly transcriptional regulation, and DNA damage repair.[50, 51] HDAC1 and HDAC2 primarily participate in the remodeling of chromatin by deacetylating histones and are also present in other transcriptional repression complexes.[50, 52] RbAp46 and RbAp48 are involved in multiple chromatin remodeling complexes and play key roles in establishing and maintaining chromatin structure.[50, 53] Structural evidence shows that the RbAp48-MTA1 interaction is essential for the integration of RbAp46/48 into the NuRD complex.[54] MTA1-3 bind to histones and modulate the higher-order chromatin structure with predominant roles in tumorigenesis and progression.[55-57] Biochemical and genetic evidence suggests that MBD3 is important for the integrity and stability of the NuRD complex, while MBD2 recruits the resulting complex onto DNA.[58, 59] Further, emerging evidence implicates the lysine-specific demethylase 1 (LSD1) contributes to histone demethylation activity into the NuRD regulatory complex.[60] More recently, the NuRD complex has also been found to be involved in gene transcription and DDR response.[9, 61]

The INO80 and SWR1 family: The INO80 and SWR1 family of ATP-dependent chromatin remodeling complexes are prototyped by the presence of an ATPase domain and Rvb1/2 proteins in

yeast (Tip49a and Tip49b in mammals)[10, 62-64] (Figure 1B). The yeast and human INO80 complex exhibits ATPase activity, which can be stimulated by DNA and nucleosome, assists in energy-driven nucleosome sliding.[10, 62, 64, 65] In contrast, the yeast SWR1 and its human homologs p400 and SRCAP (SNF2-related CBP activator protein) primarily catalyze the ATP-dependent replacement of histone H2A in canonical nucleosomes with the histone H2A variant H2A.Z in a stepwise and unidirectional fashion.[66-68] Similar to the other chromatin remodelers, the INO80/SWR1 complex is also intimately implicated in the regulation of gene transcription and genomic stability in response to DNA damage.[69-71] Despite similar overall structural organization,[72] various chromatin remodelers exerts differential function in double-strand DNA break repair and checkpoint.[73, 74]

DYSREGULATION OF CHROMATIN REMODELERS IN HUMAN CANCER

Recent advances in genomic technologies have allowed us to gain better insight into the genomic signatures underlying human cancer. A growing body of evidence suggests that dysregulation of chromatin remodelers in human cancer, such as inactivating mutation, homozygous deletion, epigenetic silencing, and overexpression, plays a fundamental role in cancer development and progression (Table 1).

Inactivating mutations: Inactivating mutations of the chromatin remodelers are common molecular abnormalities in human malignancies, generally resulting in the loss of their expression or function, and highlighting the putative tumor suppressor functions of many of the chromatin remodelers in cancer development and progression. The underlying cause of inactivating mutations could be explained by different mechanisms including gross chromosomal aberrations or loss of heterozygosity of the chromosomal region containing the tumor suppressor gene, as well as point mutations [75]. A case in point is the SWI/SNF chromatin remodelers, which have been documented

in 44 studies to be collectively mutated in about 19.6% of all human cancer.[16-18] The majority of these mutations lead to a loss of expression of the SWI/SNF chromatin remodeler proteins in cancer.

The first component of the SWI/SNF family found to be mutated in human cancer is BAF47, which was discovered to contain biallelic inactivating mutations in aggressive rhabdoid tumors.[76, 77] Consistently, BAF47 haploinsufficiency predisposes the transform rhabdoid tumors to malignancy in an animal model.[78] The underlying molecular changes that cause BAF47 gene inactivation in rhabdoid tumors include homozygous deletions and/or defective recombinations.[79] In addition, homozygous deletions of the BAF47 tumor suppressor gene are also common in some human cancer such as familial schwannomatosis,[80] epithelioid sarcomas,[81, 82] and chronic myeloid leukemia.[83] Similarly, homozygous deletions of BRG1 also result in the loss of BRG1 expression in several human cancer types including breast, lung, pancreas, and prostate cancer.[84] As expected, BRG1 re-expression in BRG1-null cells restores cellular cancerous characteristics.[84]

Accumulating evidence from whole-exome sequencing demonstrates that the SWI/SNF family members are recurrently mutated and inactivated in human cancer. Among them, BAF250A represents a commonly mutated gene in ovarian, endometrial, gastric, pancreas, breast, brain, prostate, lung, and liver cancer.[11, 18, 85-93] Similarly, inactivating mutations of genes encoding other SWI/SNF subunits such as BAF250B,[92, 94-97] ARID2[92, 93, 95, 98-102] BRG1,[75, 103-111] BAF57,[112, 113] and BAF180 [107, 114-116] also common in human cancer. In addition, CHD4 is mutated in endometrial, gastric and colorectal cancers.[90, 117, 118] Notably, mutations in the ISWI and INO80/SWR1 families of chromatin remodelers are rarely reported in human cancer.

Epigenetic silencing: In addition to inactivating mutations, other underlying mechanisms, such as epigenetic silencing through nucleosome remodeling, histones and DNA methylation, also contribute to the inactivation or loss of function of chromatin remodelers in human cancer.[119] For

example, the BRM gene is inactivated in adult lung, breast, ovary, bladder and esophagus cancers, and pediatric rhabdoid tumors,[120, 121] and epigenetic silencing may be a major mechanism behind the commonly observed BRM deficiency in such tumors.[120, 122] Accordingly, HDAC inhibitors are able to re-express BRM and suppress the formation of tumor development by BRM-null cells, and suggesting a reversible epigenetic nature of BRM expression.[120, 122] Further BRM expression and function could be reversed by other therapeutic compounds and its targets in various model systems[121, 123, 124] For instance, compounds RH02032 and GK0037 as well as the mitogen-activated protein (MAP) kinase pathway inhibitors, effectively restore BRM expression and thereby, suppress BRM-deficient cancer cell growth, suggesting that pharmacologic reversal of the BRM gene expression may be developed as a therapeutic strategy.[123, 124] In addition, BAF250B exhibits significantly reduced or loss of expression in prostate cancer tissues due to promoter hypermethylation.[125]

Overexpression: Cancer cells frequently overexpress oncogenes to drive the signaling pathways that are essential for cell survival, invasion and metastasis, and are associated with the development of drug-resistant phenotypes. One of the best examples for overexpression of the chromatin remodelers in human cancer is the Mi-2/NuRD family of chromatin remodelers. In this context, multiple subunits of the Mi-2/NuRD family of chromatin remodelers such as MTA1, MTA2, MTA3 [61, 126] and HDAC1 and HDAC2 [127-129] are overexpressed in a variety of human cancer and are associated with tumor progression, therapeutic response and patient prognosis (Table 1). In addition, multiple lines of evidence suggest that the ISWI-family chromatin remodeler Rsf1 is overexpressed in various cancers including, liver,[130] colon,[131] rectal,[132] bladder,[133] prostate,[134] ovarian,[135] oral,[136] and nasopharyngeal.[137] Moreover, elevated expression of RSF1 in such tumors is closely associated with tumor aggressiveness, poor therapeutic response and worse survival and prognosis.[132, 137-139] In

addition, SNF2H, the binding partner of the RSF1, is also overexpressed in human breast cancers and correlates with a poor prognosis through promoting breast cancer cell proliferation and invasion.[140] Furthermore, RSF1's interaction with hSNF2H plays an important role in tumor progression and the development of chemo-resistance in cancers with RSF1 overexpression.[139, 141] In addition to inactivating points, homozygous deletions and epigenetic silencing, components of the SWI/SNF family are widely overexpressed in human cancers, such as BRG1 and BRM, in primary breast cancers,[142] BAF53a in rhabdomyosarcoma tumors,[143] BAF57 in prostate cancer,[144] BAF60A in gastric cancer,[145] and BAF155 in prostate and colorectal cancer.[146, 147]

MECHANISTIC ROLE OF THE CHROMATIN REMODELERS IN CANCER

The SWI/SNF family of chromatin remodelers regulates the cell-cycle, cell death or survival, differentiation, genomic instability, and DNA repair.[148] In addition, inactivation of SWI/SNF subunits also disrupts the expression of its target genes.[149, 150] For example, the loss of BRG1 promotes tumor aggressiveness by altering nucleosome positioning at a wide range of key cancer-associated genes, and thus, dysregulating the expression of such target genes as well as resulting downstream signaling pathways.[148, 151-154] In addition, recurrent inactivating mutations in BAF47 contribute to malignant phenotypes through transcriptional attenuation of multiple tumor suppressor pathways, such as the p15,[155] p16,[155-157] p53,[158-160] and stimulation of IGFBP7,[161] as well as oncogenic signaling pathways, such as the Hedgehog-Gli pathway,[162] the cyclin D1,[163] the small GTPase RhoA,[164] the Wnt/β-catenin pathway,[165] the AKT signaling,[161] and by modulating mitosis through Aurora A overexpression.[166] In the same vein, other subunits of this family, such as BAF57,[167-170] BAF60,[171, 172] BAF180,[173] BAF250A,[174-180] BRD7,[19, 181] and BCL11B[182] also govern tumor development and progression.

One of the best studied chromatin remodelers of the ISWI family in human cancer is RSF1, which significantly promotes tumor aggressiveness [183], induces the development of chemoresistance [138, 139] and chromosomal instability[184] through the modulation of gene transcription and DNA damage response in a chromatin remodeling-dependent manner. In addition, SNF2H, a well-characterized binding partner of RSF1, is recruited to the sites of chromatin containing damaged DNA by multiple DNA-damaging proteins, and thus, regulates DNA repair.[185-188] Consequently, the loss of SNF2H may lead to defective chromatin remodeling and impaired responsiveness to DNA damaging agents.[186, 188] Similarly, both inhibition or knockdown of *SNF2L* could result in DNA damage and apoptosis.[189] Like the SWI/SNF and ISWI family of chromatin remodelers, the Mi-2/NuRD family chromatin remodelers contribute to the regulation of gene transcription and DNA damage response through a chromatin remodeling mechanism.[9, 126, 190-192] In contrast to other chromatin remodeling complexes, the mechanistic role of the INO80/SWR1 family of chromatin remodelers in human cancer remains poorly understood.

CHROMATIN REMODELERS AS CANCER THERAPEUTIC TARGETS AND BIOMARKERS

Alterations in chromatin remodelers are not only important in oncogenesis but also in the development of resistance to therapy (Table 2). An interesting example is the SWI/SNF catalytic components BRG1 and BRM which mediate chemo- and radio-resistance of human cancer cells through, at least in-part, activation of the DNA damage response.[193, 194] Consequently, targeting either BRG1 or BRM may enhance tumor cellular sensitivity to chemotherapy agents and radiotherapy.[193, 195, 196] In addition, knockdown of BAF47 in melanoma cell lines results in significant chemo-resistance,[197] while BAF155 knockdown enhances the resistance of pancreatic cancer cells to gemcitabine.[198] BAF57 is a candidate chromatin modifier for the development of

resistance to MET and ALK inhibitors in non-small cell lung cancer cells through alteration of the EGFR signaling.[199] Similarly, cancer cells lacking BAF250A and BAF250B are deficient in DNA repair and sensitive to DNA damaging agents such as ionizing radiation, cisplatin, and PARP inhibitors.[200, 201] Furthermore a reduction in the levels of BRG1, BAF250A, and BAF47 correlates with a decreased sensitivity of primary acute lymphoblastic leukemia cells to glucocorticoid therapy.[202]

Emerging data suggests that cancers with SWI/SNF-mutations may also be driven by the oncogenic effects of the basal SWI/SNF subunits. This raises the possibility of targeting such protein interactions for therapeutic development.[203] For instance, BRM plays an essential role in oncogenesis caused by the loss of BRG1, suggesting that BRM could be potentially targeted in cancer with mutated BRG1.[204-206] In the same vein, oncogenesis in the absence of BAF47 may also be dependent on BRG1 activity, and thus, approaches targeting BRG1 expression and/or activity may have therapeutic implications in BAF47-deficient tumors.[207] However, it is noteworthy to note that the loss or inactivation of BAF47 expression does not always influence the expression of BRG1-regulated genes in human cells.[208]

Among the ISWI family of chromatin remodelers, RSF1 is required for the development of chemoresistance to paclitaxel in ovarian cancer,[138, 139] and BPTF promotes resistance to BRAF inhibitors in melanoma.[209] Among the Mi2/NuRD complex, MTA1 overexpression induces cisplatin resistance in nasopharyngeal carcinoma by promoting cancer stem cells properties, and promotes docetaxel resistance in human prostate cancer cells through transcriptional repression of NR4A1.[210] In addition, HDAC1 and HDAC2 regulate the expression of P-gp via chromatin remodeling to modulate the sensitivity of drug resistant cells,[211] and CHD4 regulates homologous recombination DNA repair and CHD4-depletion confers hypersensitivity to PARP inhibitors.[212]

In general, chromatin remodeling exists in equilibrium with transcriptional silencing. For example, a key function of the SWI/SNF complex during development is prevention of the addition of the repressive H3K27me3 mark since the conditional deletion of BRG leads to the accumulation of H3K27Me3 over the genome and repression of gene transcription.[213] Likewise, NuRD-mediated deacetylation of histone H3K27 enables the addition of the repressive trimethylation mark to the same residue (H3K27me3) by PRC2.[214] Therefore, targeting the histone methyl transferases of the PRC2 complex may provide alternative strategies to influence this precious balance between chromatin remodeling and gene silencing. Indeed, the selective H3K27 metyltransferase EZH2 inhibitors, such as EPZ-6438, CPI-1205 and tazemetostat, have been entered clinical trials and show promising results in oncology (https://www.clinicaltrials.gov/ct2/results?term =EZH2&Search=Search).

PROTEIN INTERACTION INHIBITORS TARGETING REMODELING COMPLEXES – OPPORTUNITIES FOR PHARMACOLOGICAL INTERVENTION?

The complexity of chromatin remodeling complexes poses a challenge to approaching rational drug design. Along with difficulty targeting the ATP dependent catalytic domains of remodeling complexes, structural information that would enable the development of targeting methodologies and in silico approaches are still lacking. This lack of development in targeting runs counter to our understanding that is quite specific remodeling complexes are recruited onto specific sites on chromatin through interactions with small protein domains that recognize specific posttranslational modification such as lysine methylation and acetylation, arginine methylation, phosphorylation and many more.

Although the precise mechanism of remodeling complex recruitment has not yet been determined in detail, the reader domains are likely to facilitate anchoring of these complexes to an

appropriate combination of chromatin marks through specific recognition of reader domains. Remodeling complexes typically contain a number of diverse reader domains. For example the PHD finger of BPTF, which is part of the NURF complex recognizes the activating modification H3 trimethylated at lysine 4 (H3K4me3) associated with transcriptional start sites[215] and its bromodomain reads H4K16ac, which is usually associated with transcriptional activation.[216] Also bromodomains that are part of proteins in the SWI/SNF complex including BRD9, BRM and BRG recognize a variety of acetylation marks on different histones, many of which, such as H4K16ac or H2K5ac are associated with gene activation and active transcription.[217] Interestingly, BRD9 also recognizes in a specific manner butyryllysine as well as propionylated lysine residues, but the precise role of these more recently identified marks needs to be determined.[218] Recent inhibitor development efforts by the scientific and pharmaceutical community has demonstrated that many such interacting domains can be efficiently targeted by drug-like small molecules. A generic complex is illustrated in Figure 2. Interaction domains that recognize sequences containing methylated or acetylated lysines would be of particular interest for drug development.

Methyl-lysine binding proteins may recognize unmodified lysines as well as mono, di and tri-methylated lysine residues. This diverse family comprises members of the 'Royal family' (Tudor, Chromo, PWWP, and MBT domains) as well as other methyl-lysine dependent reader domains such as WD40 and PHD domains. The importance of the methyl-lysine recognition process is evident by the considerable number of mutations in these interaction motifs, in particular in PHD fingers. For instance the C-terminal PHD domain of ING (INhibition of Growth) is frequently mutated, or down-regulated in Esophageal Squamous Cell Cancer (ESCC), basal cell carcinoma, and other cancer types.[219] Computational analysis of the family of lysine methyl binding domains suggests a good druggability.[220] However, only few potent and specific inhibitors have been developed so far. The first reported potent inhibitor for this family is UNC1215. This inhibitor selectively targets

L3MBTL3, a member of the malignant brain tumor (MBT) family of transcriptional repressors.[221] Recently a potent inhibitor, OICR-9429 has been reported to inhibit the interaction of WDR5 with MLL.[222] However, while these proof-of-principle studies suggest that potent and selective inhibitors can be developed for these protein interaction domains, inhibitors targeting methyl-lysine reader domains present in remodeling complexes have not been reported so far.

EMERGING SIGNIFICANCE OF BROMODOMAINS IN CANCER

In recent years, inhibitor development programs targeting acetyl-lysine interaction domains of the bromodomain family has been quite successful and led to the generation of a comprehensive set of potent and selective inhibitors including several compounds targeting bromodomains present in remodeling complexes.[223, 224] Bromodomains are small helical acetyl-lysine reader domains with excellent druggability.[225, 226] The bromodomains are frequently present in chromatin-associated proteins that play key roles in the regulation of transcription[217] or often deregulated in cancer[227] In particular, the recent development of inhibitors against the BET family[228, 229] and the efficacy of these inhibitors in cancer led to a multitude of drug development efforts that have now entered clinical testing. BET bromodomain inhibitors that act at the target gene promotor and enhancers, will not be discussed here but are summarized in several recent excellent reviews.[224, 230]

It is important to recognize that the validity of a specific protein or a functional domain in a multi-subunit remodeling complex as a therapeutic target is not always derived from genetic studies or overexpression data. For example, BRG1 has been frequently found to be bi-allelically inactivated by homozygous deletions or combinations of deletions and mutations in several tumor types, especially in lung cancer.[203] However, BRG1 is also found to be overexpressed in tumors such as gastric,[231] prostate,[232] and skin cancer[233] and expression levels correlate with tumor progression. We suggest that targeting the components of the remodeling complexes by

conventional methods using knockdown or knockout strategies in different cell types do not necessarily provide a satisfying answers if the target protein represents a potential therapeutic target and moreover, such studies do not indicate, which domain is the most relevant for targeting such complex multicomponent systems. Therefore, the availability and development of specific tool compounds provides a crucial means to explore the therapeutic potential of these targets and validate biological hypothesis when used in cellular or animal models of disease. These challenges by these complications led to the development of selective inhibitors, so called chemical probes, that now covering most of the bromodomain tree. Useful chemical 'probes' are compounds that need to have sufficient potency and specificity as well as cellular permeability.[234] Additionally, their potential off-target effects are well characterized through screening against a variety of other unrelated pharmacologically relevant targets like kinases or GPCRs during initial developmental stages. In order to provide additional confidence in the observed biological response an effort has been made to have more than one specific inhibitor for a given target. For example, although both BAZ2-ICR and GSK2801 inhibit the interaction of BA2A/B with chromatin, they provide alternative scaffolds to target these proteins. In addition, a negative control compound chemically related to GSK2801 presents further reassurance that the observed biological effects are indeed due to targeting the bromodomains of BAZ2A/B (Figure 3). Several complementing inhibitors are also available for the bromodomains of the histone acetyltransferases EP300/CREBBP: CBP-30 and I-CBP112 complements each other and have helped to elucidate the role of CREBBP in inflammatory disorders[235] and leukemia[236] (Figure 3). In general, members of the BRPF family are scaffolding proteins with an essential function to recruit histone acetyl transferases to chromatin. Several probes from alternative chemical scaffolds targeting either the whole family (pan-inhibitors OF-1 and NI-57) or a specific family member (PFI-4) have been developed (Figure 3).

Several potent inhibitors are being developed for bromodomains present in the remodeling complexes. The first set of inhibitors has been developed for bromodomains present in BAZ2A/B protein of the NoRC complex. The family member BAZ2A associates with ATPase SNF2h to form the nucleolar remodeling complex (NoRC).[237] NoRC associates with the regulation of the expression of noncoding RNAs and establishes a heterochromatic structure at centromeres and telomeres,[238] a function that has been linked to the BAZ2A bromodomain.[239] BAZ2A is required to maintain the growth of prostate cancer cells and its high expression levels associates with the recurrence of prostate cancer.[240] The closely related BAZ2B is a less studied family member but is overexpressed in pediatric B cell acute lymphoblastic leukemia (B-ALL) and high BAZ2B levels are associated with poor outcome of B-ALL patients. However, so far only the synthesis of two chemically diverse inhibitors have been reported and the biological consequences of inhibiting the BAZ2A/B bromodomains and their potential role in cancer remains to be elucidated.[241, 242]

A strong correlation of protein expression and poor prognosis exists for the bromodomain protein and ATPase ATAD2, which functions as an ATP dependent co-regulator of transcription factors such as c-Myc, estrogen and androgen receptors and E2F transcription factors.[243-245] ATAD2 is overexpressed in a large diversity of tumors, particularly in gastrointestinal tumors, large B-cell lymphoma, hepatocellular carcinoma and breast and lung cancers,[246-249] and correlates well with a poor prognosis in patients with breast or lung cancer and associates with a distant recurrence.[250] Recently potent inhibitors for this interesting bromodomain protein have been reported, but similar to BAZ2A/B inhibitors, their biological evaluation is still lacking.[251]

As described above, SWI/SNF complexes exhibit chromatin remodeling activity and because component of SWI/SNF are mutated or lost at high frequency in tumors, this remodeling complex has attracted considerable attention in oncology. SWI/SNF contain either the catalytic remodeling subunit BRM (SMARCA2) or BRG1 (SMARCA4), which alters chromatin structure in an ATP-

dependent fashion resulting in an "open chromatin" competent for interactions with transcription factors.[252] Both catalytic subunits of SWI/SNF contain a bromodomain, offering an opportunity for inhibitor development. A subclass of SWI/SNF complex, PBAF, contains the polybromo protein (PB1 or BAF180) which is required for ligand-dependent trans-activation by nuclear hormone receptors. PB1 contains six evolutionary conserved bromodomain modules together with two methyl-lysine binding BAH domains, suggesting that anchoring PBAF to chromatin is the main function of the PB1 scaffolding protein. PB1 has been shown to play a key role in the regulation of cell cycle and senescence[253-255] as well as in the mediation of vitamin D receptor-dependent transcription. Mice lacking PB1 exhibit defects in heart development due to impaired epithelial-to-mesenchymal-transition (EMT) and arrested maturation of the epicardium as a result of the down-regulation of the growth factors TGF, FGF and VEGF.[256, 257]

Recent loss-of-function genetic studies suggest that SMARCA2 is an essential gene for cell survival in SMARCA4-deficient lung cancer, making a compelling case to target SMARCA2 in such tumors.[204-206] However, the requirement of the bromodomain in SMARCA2 has not been demonstrated. Using the selective inhibitor PFI-3 developed by our laboratory and Pfizer (Fedorov et al, in press) a recent study targeting the SMARCA2/4 bromodomain did not result in cytotoxicity or inhibition of clonogenic growth in SMARCA4-deficient tumors. In contrast, the helicase domain convincingly phenocopied the genetic loss-of-function experiments.[258] The SWI/SNF complex harbors a large diversity of protein interaction domains that anchor this large remodeling complex to specific sites containing a certain set of post-translational modifications. Hence, PFI-3 does not appear to target bromodomains that are critical for the recruitment of SWI/SNF to the chromatin as PFI-3 is not able to displace the endogeneous SMARCA2/4 from chromatin, suggesting the role of another interaction domain or a combination of interaction domains for chromatin targeting the SWI/SNF complex. Additional targeting possibilities include bromodomains present on PB1 or in

BRD7/9. Two structurally diverse inhibitors targeting the BRD7/9 bromodomains have been recently reported. It would be interesting to learn whether these inhibitors alone or in combination with PFI-3 would displace the SWI/SNF complex from chromatin and result in synthetic lethality as reported in the genetic loss-of-functional studies.[259, 260] An alternative strategy would be to target the SWI/SNF complex for degradation using phtalimide adducts.[261]

In closing, targeting chromatin remodeling complexes has only recently emerged as a new area in chemical biology. Thus, more studies need to be carried out in order to assess the potential usefulness of developed tool compounds either as single-agent or combination therapies with conventional chemotherapeutic treatment or radiotherapy in oncology. However, the central role of remodeling complexes in tumorigenesis, tumor maintenance, and progression makes these large protein complexes interesting targets for the development of future treatment strategies.

CONFLICT OF INTEREST STATEMENT

The authors declare no any potential conflict of interest.

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Figure legends

Figure 1. Four families of chromatin remodelers. **A**, The domain architecture of the catalytic subunits of four major classes of chromatin remodelers. Each ATPase subunit contains a distinctive ATPase domain that is split into two parts: a DEAD-like helicases superfamily (DExx) domain and

a helicase superfamily c-terminal (HELICc) domain. Other specific domains for various chromatin remodeler families include the bromodomain (bromo) in SWI/SNF family, the HAND-SANT-SLIDE (HSS) domain in ISWI family, the chromodomains (chromo) in the Mi-2/NuRD family, and the helicase/SANT-associated (HSA) domain in both SWI/SNF and INO80/SWR1 families. Illustrated domains are not in scale with the size of the proteins. **B,** The ATPase Subunits and other core subunits of four families of human chromatin remodelers.

Figure 2: **Reader domains in chromatin remodeling complexes. A**, Generic composition of the SWI/SNF complex. Targeted domains as well as developed inhibitors are indicated. As discussed, the complex may contain tissue specific components. Here a generic complex is shown but not isoforms are included for clarity. Reader domains are shown as symbols as indicated in the figure capture. **B**, NoRC complex containing the bromodomain protein BAZ2A/B. Inhibitors targeting reader domains are shown in red and the targeted domains are indicated.

Figure 3: **Chemical probes available targeting reader domains of protein acetylation.** A large number of inhibitors have now been developed for BET bromodomains and therefore, only 2 examples are shown in the figure. Inhibitor names are shown in black (bold) and targeted bromodomains are shown in red. For protein containing more than one bromodomain the names has been expanded by a number indicating the position for the bromodomain from the N-terminus, e.g. PB1(1) represents the first bromodomain in PB1). Name of the subfamilies is according to Filippakopoulos *et al.*[224]

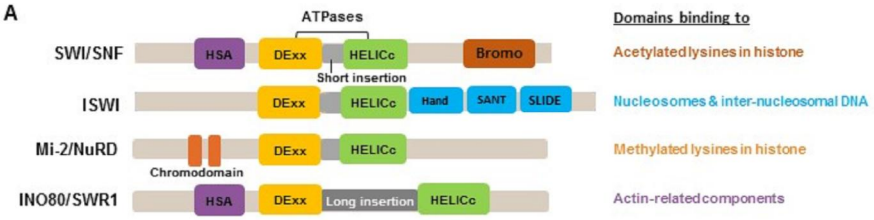
Table 1. Dysregulation of chromatin remodelers in human cancer

Dysregulation	Remodeler family	Subunits	Tumor types
Inactivating mutation	SWI/SNF	BRG1	Renal,[107] ovarian cancer,[105, 106] Burkitt lymphoma[108]
		BAF180	Renal cancer[116]
		BAF200	Lung cancer[102]
		BAF250A	Liver,[88] renal,[107] endometrial cancer,[90] Burkitt lymphoma[108]
	Mi-2/NuRD	CHD4	Endometrial cancer[90, 117]
Deletions	SWI/SNF	BAF47	Malignant rhabdoid tumors,[77] chronic myeloid leukemia,[83] rhabdomyosarcoma,[262] epithelioid sarcoma[81]
		BRG1	Oral,[263] pancreatic cancer,[111] rhabdoid tumor[75]
		BRM	Pancreatic cancer[111]
		BAF180	Pancreatic cancer[111]
		BAF250B	Pancreatic cancer[111]
Epigenetic silencing	SWI/SNF	BRM	Various types of human cancer[120-123, 264]
Overexpression	SWI/SNF	BRG1	Prostate cancer,[265] melanoma[233, 266]
		BAF53a	Rhabdomyosarcoma[143]
		BAF57	Prostate cancer[144]
		BAF155	Prostate cancer[146]
	ISWI	RSF1	Nasopharyngeal,[137] oral,[136] liver,[130] gallbladder,[267] rectal,[132] colon,[131] bladder,[133] ovarian,[135] prostate cancer[134]
		SNF2H	Breast,[140] ovarian cancer[141]
		BPTF	Melanoma[269]
	Mi-2/NuRD	MTA1	Nasopharyngeal,[268] oral and tonsil,[269] breast,[270] esophageal,[271] gastric,[272] liver,[273] gallbladder,[274] colon,[275] colorectal,[272] pancreatic,[276] lung,[277] prostate,[278] endometrial,[279] ovarian,[280] cervical cancer[281]
		MTA2	Breast[282] and liver cancer[283]
		MTA3	Non-small cell lung cancer[284, 285]
		HDAC1	Gliomas,[286] thyroid,[287] gastric,[288] colorectal,[128] renal,[289] prostate,[129] ovarian and endometrial cancer,[290] and lymphomas[291, 292]
		HDAC2	Gliomas,[286] thyroid,[287] gastric,[288] colorectal,[128] renal,[289] pancreatic,[293] prostate,[129] ovarian and endometrial,[290] lymphoma[294]

Table 2. Chromatin remodelers in therapeutic response of human cancer

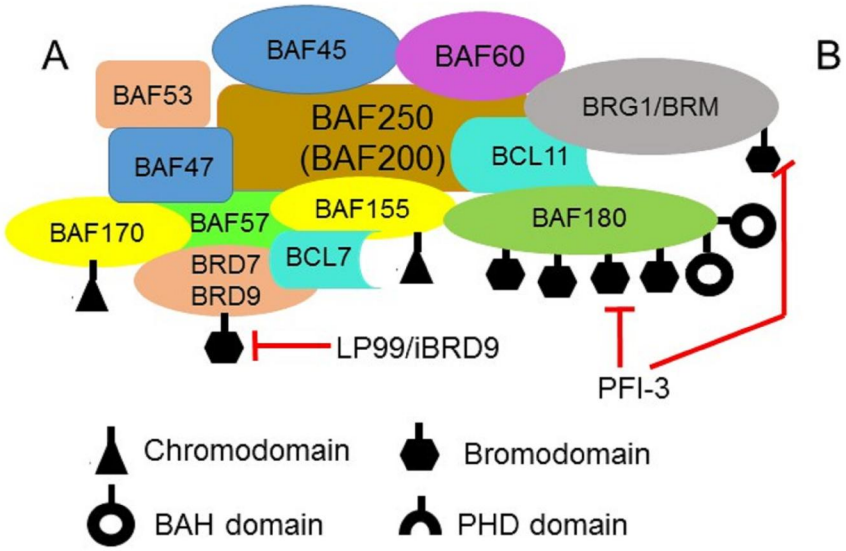
Remodeler family	Subunits	Therapeutic response	Tumor types
SWI/SNF	BRG1	Resistance to cisplatin	Lung and head/neck cancer[196]
	BRM	Resistance to cisplatin	Lung and head/neck cancer[196]
	BAF47	Sensitivity to doxorubicin, daunorubicin, and epotoside	Breast cancer[295]
	BAF57	Sensitivity to MET and ALK inhibitors	Non-small cell lung cancer[199]
	BAF155	Sensitivity to gemcitabine	Pancreatic cancer[198]
	BAF250A	Resistance to ionizing radiation and cisplatin	Lung cancer and osteosarcoma[201]
		Resistance to PARP inhibitor	Colon cancer[296]
	BAF250B	Resistance to ionizing radiation and cisplatin	Lung cancer and osteosarcoma[201]
ISWI	RSF1	Paclitaxel resistance	Ovarian cancer[138, 139]
	BPTF	Resistance to BRAF inhibitors	Melanoma[209]
Mi-2/NuRD	CHD4	Resistance to PARP inhibitors	Breast cancer[212]
		Sensitivity to cisplatin	BRCA2-mutant cancer[297]
		Sensitivity to daunorubicin and cytarabine	Acute myeloid leukemia[298]
	MTA1	Cisplatin resistance	Nasopharyngeal carcinoma[299]
		Docetaxel resistance	Prostate cancer[210]
	HDAC1	Sensitivity to vinblastine, oxaliplatin, fluorouracil and mitomycin C	Colorectal cancer[211]
	HDAC2	Resistance to the topoisomerase II inhibitor etoposide	Pancreatic adenocarcinoma[293]
		Sensitivity to vinblastine, oxaliplatin, fluorouracil and mitomycin C	Colorectal cancer[211]

A



B

	Human SWI/SNF		Human ISWI			Human Mi-2/NuRD	Human INO80		
	BAF	PBAF	NURF	ACF	CHRAC		INO80	SWR1	
								Tip60	SRCAP
ATPases	BRG/BRM	BRG	SNF2L	SNF2H	SNF2L	CHD3/CDH4	hINO80	P400	SRCAP
Other core subunits	BAF45 BAF47 BAF53 BAF57 BAF60 BAF155 BAF170 BAF250 BRD9 BCL7 BCL11	BAF45 BAF47 BAF53 BAF57 BAF60 BAF155 BAF170 BAF180 BAF200 BRG7	BPTF RbAP46 RbAP48	hACF1	BPTF RbAP46 RbAP48	HDAC1/2 MBD2/3 MTA1-3 RbAp46/48 LSD1	Tip49a Tip49b BAF53a Arp5,8 hles2 hles6	Tip49a Tip49b BAF53a TRRAP Tip60	Tip49a Tip49b BAF53a Arp6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BAF60
BAF53
BAF250
(BAF200)
BRG1/BRM
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BAF155
BAF180
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BRD9
LP99/iBRD9
PFI-3
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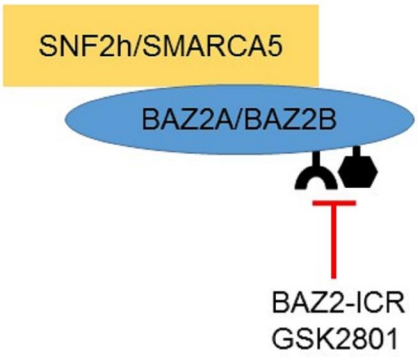
Bromodomain
BAH domain
PHD domain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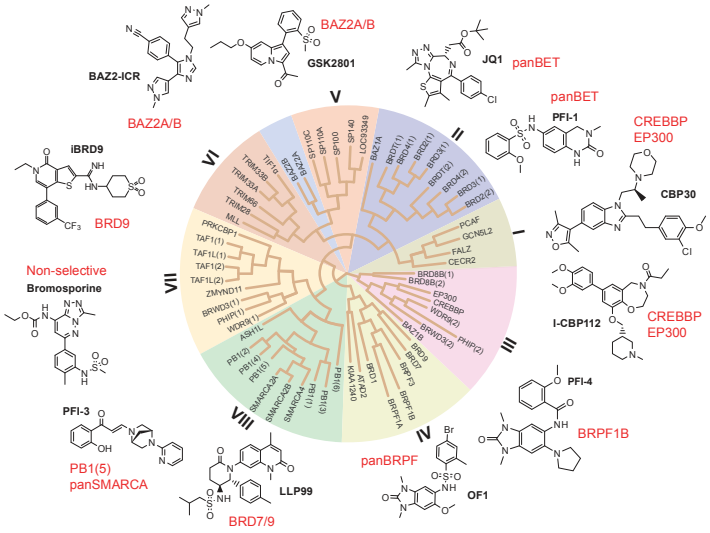
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BRD9
CBP30
Non-selective
Bromosporine
I-CBP112
CREBBP
EP300
PFI-4
BRPF1B
PFI-3
PB1(5)
panSMARCA
LLP99
BRD7/9
panBRPF
OF1