

Molecular Pathways: SWI/SNF (BAF) Complexes Are Frequently Mutated in Cancer—Mechanisms and Potential Therapeutic Insights

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Abstract

SWI/SNF chromatin remodeling complexes are pleomorphic multisubunit cellular machines that utilize the energy of ATP hydrolysis to modulate chromatin structure. The complexes interact with transcription factors at promoters and enhancers to modulate gene expression and contribute to lineage specification, differentiation, and development. Initial clues to a role in tumor suppression for SWI/SNF complexes came over a decade ago when the gene encoding the SMARCB1/SNF5 core subunit was found specifically inactivated in nearly all pediatric rhabdoid tumors. In the last three years, cancer-genome sequencing efforts have revealed an unexpectedly high mutation rate of SWI/SNF subunit genes, which are collectively mutated in 20% of all human cancers and approach the frequency of p53 mutations. Here, we provide a background on these newly recognized tumor suppressor complexes, discuss mechanisms implicated in the tumor suppressor activity, and highlight findings that may lead to potential therapeutic targets for SWI/SNF-mutant cancers. *Clin Cancer Res*; 20(1); 21–27. ©2013 AACR.

Background

Chromatin and SWI/SNF complexes

Nuclear DNA wrapped around a histone octamer constitutes the nucleosome, the basic unit of chromatin. Further compaction of DNA through progressive coiling not only provides an organizational structure for the two meters of DNA contained within each cell but also presents an access barrier to the transcriptional machinery. Numerous chromatin-modifying complexes exist in mammalian cells, and these are intimately involved in processes that require DNA access such as transcription, replication, and repair. These complexes can be grouped into two classes: those that covalently modify nucleosomes and those, like the SWI/SNF complex, that consume ATP to mobilize nucleosomes and modulate chromatin compaction.

SWI/SNF complexes are evolutionarily conserved and were originally identified in yeast. Genes encoding SWI/SNF subunits were revealed in screens of yeast for defects in mating type SWitching and in sucrose metabolism (Sucrose NonFermentable; SNF; ref. 1). Mammalian SWI/SNF complexes are also referred to as BAF (BRG1-associated factors) complexes in recognition that mammalian complexes contain additional subunits not found in the yeast complex,

and therefore the extent to which activities are conserved remains unclear (2). Mammalian SWI/SNF complexes (herein referred to simply as SWI/SNF complexes) are enriched at promoters and enhancers of active genes and have been shown to contribute to the regulation of differentiation and proliferation across many lineages (3–5). SWI/SNF complexes are large, approximately 2 MDa, and composed of 12 to 15 subunits (2). These complexes are composed of one of the two mutually exclusive catalytic ATPase subunits: SMARCA2 (Brahma or BRM) or SMARCA4 (BRM/SWI2-related gene 1, or BRG1), and a set of widely expressed core subunits that include SMARCB1 (SNF5, INI-1 or BAF47), SMARCC1 (BAF155), and SMARCC2 (BAF170; ref. 2). In addition, SWI/SNF complexes also contain a large number of lineage-restricted subunits often encoded by multigene families (Table 1). Recent work has demonstrated that these complexes may further contain additional subunits not previously appreciated (6). Considering the large number of variant subunits, it has been estimated that several hundred versions of SWI/SNF complexes may exist, each with a conserved core of subunits but containing distinct combinations of variant subunits (7).

The precise biochemical function of SWI/SNF complexes remains somewhat unclear. *In vitro* assays have clearly demonstrated that the complexes are capable of mobilizing and ejecting histone octamers on DNA (8). Functional studies performed to evaluate biochemical activity of SWI/SNF complexes in living cells have implicated the complexes in the establishment of nucleosome occupancy and phasing at promoters and enhancers at a subset of active genes (3–5), as well as in DNA repair processes (9–11). Recent studies have begun to demonstrate that although

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Table 1. Summary of the SWI/SNF complex subunits and mutations in cancers

Subunit	Aliases	Function	Mutated in human cancer
ARID1A	BAF250A	Variant subunit, BAF complex only	Ovarian, hepatocellular, bladder, gastric, endometrioid, pancreatic, colon, lung, neuroblastoma, Burkitt lymphoma
ARID1B	BAF250B	Variant subunit, BAF complex only	Melanoma, neuroblastoma, hepatocellular, pancreatic, liver
PBRM1	BAF180	Variant subunit, PBAF complex only	Renal cell carcinoma, breast, gastric, pancreatic
ARID2	BAF200	Variant subunit, PBAF complex only	Melanoma, hepatocellular, pancreatic
SMARCA2	BRM	Catalytic ATPase subunit	Lung, colon, breast
SMARCA4	BRG1	Catalytic ATPase subunit	Lung, medulloblastoma, Burkitt lymphoma
SMARCB1	SNF5, INI1	Core subunit	Rhabdoid tumor, familial schwannomatosis
SMARCC1	BAF155	Core subunit	
SMARCC2	BAF170	Core subunit	
SMARCD1/2/3	BAF60A/B/C	Variant subunit	Breast
SMARCE1	BAF57	Variant subunit	Spinal meningioma
ACTL6A/B	BAF53A/B	Variant subunit	
PHF10	BAF45A	Variant subunit	
DPF1/2/3	BAF45B/C/D	Variant subunit	
ACTB	β-Actin		

SWI/SNF complexes may be ubiquitously expressed, individual cells contain a selected set of variant subunits that contribute to lineage-specific targeting and determination of cell fate (3–5). Perhaps some of the clearest evidence has come from studies on neural differentiation, which showed that SWI/SNF complex composition undergoes an essential subunit switch during the progression from neural progenitors to postmitotic neurons (12). Similarly, embryonic stem cells have been shown to contain a distinctive assembly of SWI/SNF subunits essential for embryonic stem cell maintenance and pluripotency (13). Such interaction with and recruitment of lineage-specific transcriptional regulators seem to be a central mechanism by which SWI/SNF complexes contribute to lineage specification. For example, MyoD, the muscle determination factor, can be directly incorporated into SWI/SNF complexes, which then results in transcription of MyoD target genes (14). Similarly, Olig2 has been shown to physically associate with the SWI/SNF complex at oligodendrocyte-specific enhancers during differentiation (15). SWI/SNF complexes may contribute specificity to transcription factor interactions and targeting via subunits that contain DNA-binding and histone-binding domains, including high-mobility group, ARID, HSA, PHD, and bromodomains, which are found in both core and variant SWI/SNF subunits (7). Thus, regulation of gene expression and cell lineage specification via direct recruiting or interaction with key transcription factors may be a central function of SWI/SNF complexes (Fig. 1).

SWI/SNF complex mutations in cancer

In 1998, specific biallelic inactivating mutations of the core SWI/SNF subunit SMARCB1 (SNF5/INI1/BAF47) were identified in the vast majority of cases of rhabdoid tumors, highly aggressive and lethal cancers arising in the kidney,

brain, and soft tissues of young children (16, 17). The *bona fide* tumor suppressor properties of SMARCB1 were subsequently demonstrated in genetically engineered mouse models: although homozygous loss results in embryonic lethality, heterozygous mice are viable and 30% develop cancers that closely resemble human rhabdoid tumor (18–20). In these tumors, the wild-type allele has been spontaneously inactivated so, as in humans, the tumors completely lack SMARCB1. To bypass embryonic lethality associated with homozygous loss, conditional SMARCB1 alleles were generated. Conditional homozygous inactivation in postnatal mice results in cancer in 100% of mice at a median onset of only 11 weeks, a remarkably rapid rate of onset for inactivation of a single gene (21). In comparison, biallelic inactivation of p53 leads to cancer at a median of 22 weeks.

Although rhabdoid tumors served as the initial clue linking mutation of genes encoding SWI/SNF subunits to cancer, recent cancer-genome sequencing studies have revealed a much broader role (22–24). Only 3 years ago, two papers reported that more than 50% of ovarian clear cell carcinomas contain inactivating mutations in ARID1A (25, 26), which encodes a variant subunit of the complex. Subsequently, frequent mutations of SWI/SNF complex subunits have been identified in a variety of human cancers (Table 1; selected references and summary reviews: 6, 22–24, 27–46). So far, at least eight genes encoding SWI/SNF complex subunits have been found to be recurrently mutated in a variety of cancers including subsets of lung, breast, stomach, liver, pancreas, kidney, bladder, skin, and brain cancers. These mutations are predominantly loss of function (6, 22–24, 27). Interestingly, although SMARCB1 is always biallelically mutated, other subunits are often heterozygously mutated, raising the possibility of haploinsufficiency for these subunits in tumor suppression (6, 27).

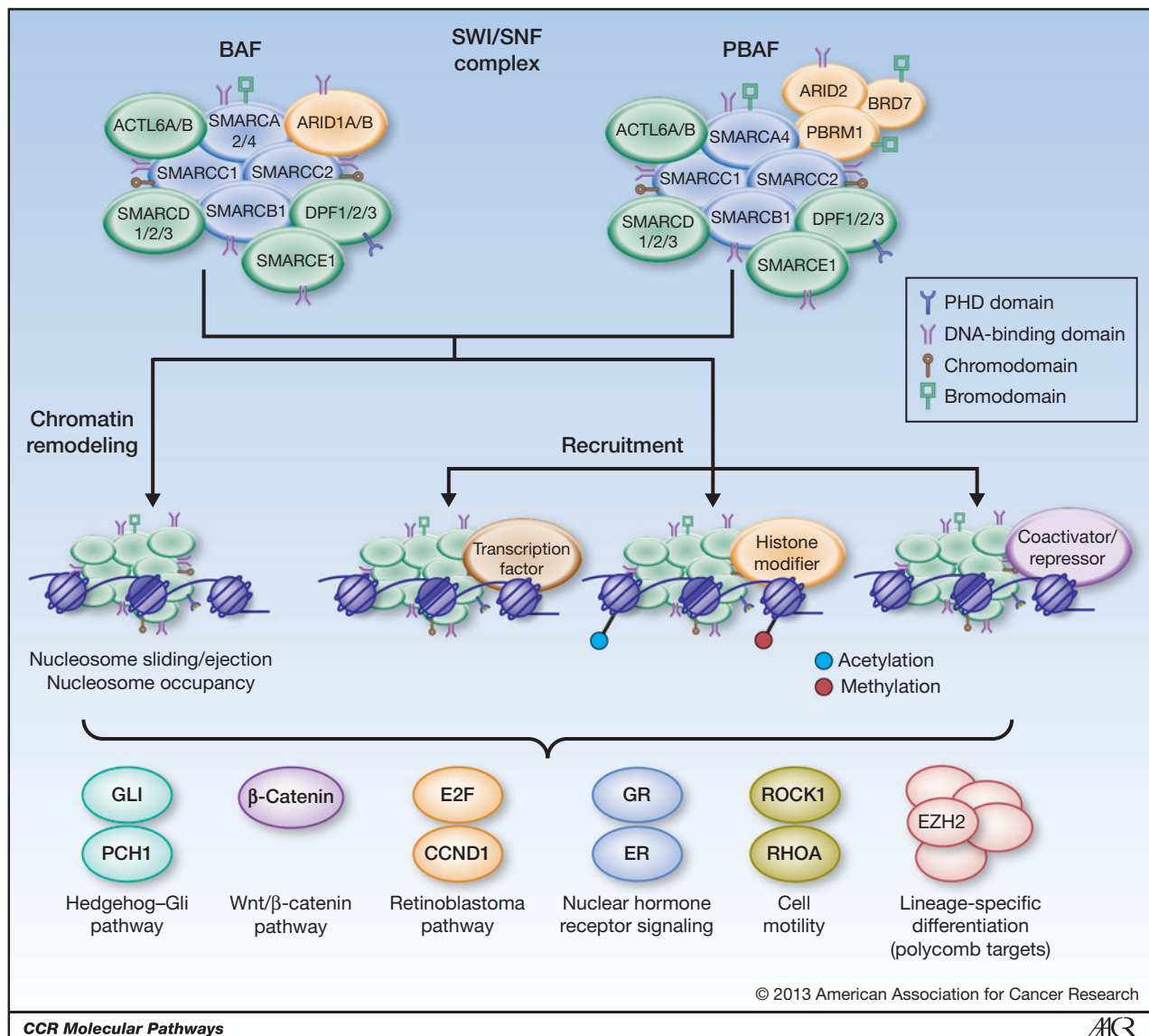


Figure 1. SWI/SNF functions in chromatin modulation and tumor suppression. Two subclasses, BAF and PBAF, of many variants of SWI/SNF complexes are shown. BAF and PBAF differ in composition of the subunits that are shown in orange. Core subunits are shown in blue. Further diversity is derived from the subunits shown in green as these are all encoded by multigene families, each yielding a slightly different amino acid sequence. These diverse complexes then make specific contributions to targeting of chromatin remodeling and transcriptional control. Several of the pathways that have been implicated in tumor suppression are shown at the bottom.

Thus far SMARCB1 and SMARCA4 have been validated to have *bona fide* tumor suppressor function using genetically engineered mouse models (18–21, 47), whereas others remain to be tested. Collectively, genes encoding SWI/SNF complex subunits have now been recognized as one of the most commonly mutated targets in human cancer, being thus far detected in 20% of human cancers (6, 48).

Genetics or epigenetics?

Despite the prevalence of SWI/SNF complex mutations in cancer, insight into the mechanisms underlying tumor suppression and the reason for the differing cancer spectrum associated with each subunit is still in its infancy. In

addition to a role in transcriptional regulation, several studies have linked the complex to DNA repair including nucleotide excision repair, double-strand break repair, and DNA decatenation (9–11, 49). Consequently, it has been a question of great interest whether the tumor suppressor activity of the complex arises via a role in the control of transcriptional programs or whether it is derived from a role for the complex in protecting genome integrity. Perhaps providing substantial insight, rhabdoid tumors are diploid, chromosomally stable, and contain a marked paucity of aberrations detectable by single-nucleotide polymorphism arrays, other than loss of SMARCB1 itself (50). More recently, exome sequencing of human rhabdoid tumors revealed

that despite their highly aggressive nature, these cancers contain an extremely low rate of mutations (51), one of the lowest ever measured (52). Across 35 of these SMARCB1-deficient cancers, there were essentially no other recurrent mutations and in two of the cancers, there were no other identified mutations at all. The same conclusion was reached in other studies as well (53, 54). Given the paucity of other mutations and the extremely rapid onset of cancer in mouse models, these findings seem to suggest that SMARCB1 deficiency may not cause cancer via defects in DNA repair but rather due to epigenetic alterations such as disruption of chromatin-based contributions to control of cell fate. Given that at least eight subunits of the SWI/SNF complex are recurrently mutated in cancer, it is tempting to speculate that the general mechanism is likely shared. However, although evidence seems to suggest that SMARCB1 loss drives cancer via an epigenetic mechanism, whether a similar mechanism underlies cancer associated with ARID1A, SMARCA4, PBRM1, and other subunit mutations remains to be determined. Interestingly, mutations in more than one SWI/SNF subunit gene can occur in primary tumors, perhaps reflecting both haploinsufficiency and compound heterozygous effects (6, 47).

Clinical-Translational Advances

As increasing evidence has linked mutation of the SWI/SNF complex to a variety of human cancers, there has been a growing desire to identify vulnerabilities created by SWI/SNF mutation. Unlike some activating oncogene mutations, such as BCR-ABL fusion or EGF receptor (EGFR) mutation, which can be directly therapeutically targeted, the majority of SWI/SNF complex mutations are inactivating. Thus, the proteins are absent and cannot be directly targeted. Thus, a goal should be to achieve a better understanding of the mechanisms underlying transformation and dependencies created by mutation of SWI/SNF subunits. Indeed, early studies on the basic function of SWI/SNF complexes have revealed potential vulnerabilities currently being translated.

Pathways affected by SWI/SNF mutations

Some of the earliest studies of cancer-associated gene mutations, identification of genes activated by chromosomal translocation in acute leukemias, revealed the theme that these genes were often transcription factors that were master regulators of lineage development such that their forced overexpression resulted in perturbation of lymphoid development and predisposition to transformation. In its role of interacting with transcription factors to facilitate lineage-specific development, it is conceivable that mutation of SWI/SNF complexes predisposes to cancer in much the same way—via disruption of development, proliferation, and differentiation pathways. However, relevant target pathways are only beginning to be characterized.

One of the challenges for the field is that although SMARCB1 was recognized as a tumor suppressor 15 years

ago, other subunits have only been linked to cancer recently. Consequently, mechanisms underlying the role of SMARCB1 in tumor suppression have been more extensively investigated. However, it remains to be determined the extent to which these mechanisms are shared with cancers driven by other SWI/SNF subunit mutations. Collectively, a shared mechanism of perturbation of SWI/SNF function seems likely. However, as the spectrum of cancer types associated with each subunit varies, the specific pathways affected may depend upon the subunit mutated. Ultimately, additional studies will be needed to determine the extent to which vulnerabilities caused by mutation of one SWI/SNF subunit gene extend to others.

The tumor suppressor activity of SWI/SNF complexes was first linked to the retinoblastoma tumor suppressor pathway when inactivation of SMARCB1 was shown to downregulate p16INK4A expression, a cyclin-dependent kinase (CDK) inhibitor that regulates the retinoblastoma pathway (55–59). SWI/SNF complexes can also bind to retinoblastoma itself and facilitate the repression of retinoblastoma target genes, such as *E2Fs* and *CCND1* (60–62), suggesting a contribution of SWI/SNF complexes to cell-cycle regulation. Some, but not all, studies have found high-level cyclinD1 expression in rhabdoid tumor, and pharmacologic inhibitors of cyclin D1 have been reported effective in reducing the growth of rhabdoid tumor cell lines *in vitro* and *in vivo* (50, 63–66). Collectively, these findings have led to a phase I/II clinical trial of rhabdoid tumors using CDK4 inhibitors (<http://clinicaltrials.gov/show/NCT01747876>).

A number of other target pathways and functions have been implicated in cancer driven by SWI/SNF mutations. For example, SWI/SNF complexes have been implicated in the control of cell motility via regulation of RhoA (67) and actin cytoskeletal organization (68). SWI/SNF complexes can also directly interact with MYC, an oncogene frequently overexpressed in cancer (69), and SMARCB1-deficient rhabdoid tumors show activation of MYC programs (70, 71). SWI/SNF complexes interact with nuclear hormone receptors, such as glucocorticoid receptors, estrogen receptors, and retinoic acid receptors (72). Clinical studies found that decreased levels of SWI/SNF subunits SMARCB1/SMARCA4/ARID1A correlate with steroid resistance in pediatric acute lymphoblastic leukemia, with the underlying mechanism remaining unknown (73). SWI/SNF complexes have also been implicated in the regulation of the Wnt/ β -catenin pathway. BRG1 deletion results in downregulation of the Wnt receptor family and degradation of β -catenin (74). The telomerase protein component TERT (telomerase reverse transcriptase) can also interact with BRG1, to modulate the Wnt/ β -catenin pathway (75), and another study reported that loss of SMARCB1 results in β -catenin hyperactivation (76). SWI/SNF complexes also directly interact with Gli1, the effector of Hedgehog signaling and in rhabdoid tumor cells, loss of SMARCB1 leads to an aberrant activation of the Hedgehog–Gli pathway (77). These results suggest that SWI/SNF complexes directly regulate the canonical Wnt/ β -catenin and Hedgehog pathways. Collectively, SWI/SNF complexes have been implicated in the control of

a number of cancer-related transcriptional pathways, some of which may provide therapeutic potential (Fig. 1). Via such investigations, a theme is also emerging that SWI/SNF mutations may directly affect genes and pathways at the level of chromatin, and thus uncouple pathways from upstream canonical control. For example, cancers in which the Hedgehog pathway is activated by mutation of the PTCH receptor are sensitive to blockade of SMO downstream in the signaling cascade. In contrast, SMO inhibitors are unable to block Hedgehog signaling in SMARCB1-mutant cancers. Similarly, the Wnt/ β -catenin can be inhibited at multiple levels. However, none of these upstream inhibitors have an effect upon the Wnt pathway in SMARCB1-mutant cancers where a key contributor seems to be a failure of the constitutive Wnt repressor TCF to bind target DNA in the absence of SMARCB1 thus resulting in spontaneous Wnt signaling uncoupled from canonical pathway control. Although still early in the understanding of mechanism, it is tempting to speculate that chromatin remodeler mutations, such as SWI/SNF, may provide an explanation for findings such as the discrepancy that EGFR-mutant cancers are susceptible to EGFR blockade, whereas cancers that show transcriptional activation of the EGFR pathway, but lack mutations in EGFR itself, are unresponsive. Consequently, disruption of chromatin structure may have the potential to directly alter pathway signaling. Therefore, gaining insight into the function of SWI/SNF complexes in transcriptional control may offer novel modulation approaches of cancer-related pathways.

Antagonism of SWI/SNF complex and polycomb complex—targeting EZH2?

High mutation rate of SWI/SNF chromatin remodelers in a large variety of cancer suggests a chromatin-based epigenetic mechanism that drives cancer development by regulating chromatin structure. Therefore, mutations of SWI/SNF complexes likely lead to an aberrant chromatin landscape, providing the driving force of oncogenesis. Recent discoveries describing an epigenetic antagonism between Polycomb and the SWI/SNF complex support this model (70, 78). Loss of SMARCB1 was found to cause elevated levels of EZH2 and H3K27me3 at PcG target genes thus leading to broad repression of these targets (70). Another study in embryonic stem cells found complex interactions between SWI/SNF and Polycomb complexes, at times antagonistic and at others cooperative (4). In a genetically engineered *in vivo* tumor model, inactivation of EZH2 completely blocked tumor onset driven by SMARCB1 loss (70). This discovery suggested EZH2 as a target for SMARCB1-mutant cancers. In contrast with these findings, another group found that knockdown of SMARCB1 does not affect the level of EZH2 (79), raising the possibility that antagonism between SMARCB1 and EZH2

might be complex and cell-context dependent (79, 80). Nonetheless, a recent study reported that targeted pharmacologic inhibition of EZH2 results in durable regressions in genetically altered malignant rhabdoid tumors, suggesting this as a potential new treatment for rhabdoid tumor (81), stimulating interest in therapeutic trials for rhabdoid tumor. Whether antagonism between SMARCB1 and EZH2 extends to other SWI/SNF subunits and associated cancers needs to be further investigated.

Summary/Prospective

Cancer-genome sequencing studies have identified genes encoding subunits of the SWI/SNF chromatin remodeling complexes as being frequently mutated across a wide variety of cancers. However, identification of these links is largely recent and the mechanisms by which these complexes act as tumor suppressors are only just beginning to be elucidated. Although some evidence indicates that these complexes may contribute to DNA repair, involvement of these complexes in chromatin-based epigenetic regulation has been implicated in their tumor suppressor activity. Ultimately, understanding the fundamental biology of SWI/SNF complexes, such as roles in the regulation of chromatin structure/landscape, the biochemical contributions of different subunits, and activity in modulating transcription, offer promise for novel therapeutic approaches to SWI/SNF-mutant cancers.

Disclosure of Potential Conflicts of Interest

C.W.M. Roberts has commercial research grant and is consultant/advisory board member of Novartis Institutes for Biomedical Research. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: X. Wang, C.W.M. Roberts

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): X. Wang

Writing, review, and/or revision of the manuscript: X. Wang, J.R. Haswell, C.W.M. Roberts

Study supervision: C.W.M. Roberts

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