Published in final edited form as:

Cancer Genet. 2014 September ; 207(9): 365–372. doi:10.1016/j.cancergen.2014.04.004.

Mechanisms by which SMARCB1 loss drives rhabdoid tumor growth

Kimberly H. Kim^{1,2,3,4} and Charles W. M. Roberts^{1,2,3,4}

¹Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA

²Division of Hematology/Oncology, Children's Hospital Boston MA, USA

³Department of Pediatrics, Harvard Medical School, Boston MA, USA

⁴Broad Institute of Harvard and Massachusetts Institute of Technology, Boston, Massachusetts, USA

Abstract

SMARCB1 (INI1/SNF5/BAF47), a core subunit of the SWI/SNF (BAF) chromatin-remodeling complex, is inactivated in the large majority of rhabdoid tumors and germline heterozygous *SMARCB1* mutations form the basis for rhabdoid predisposition syndrome. Mouse models validated *Smarb1* as a bona fide tumor suppressor as *Smarb1* inactivation in mice results in 100% of the animals rapidly developing cancer. SMARCB1 was the first subunit of the SWI/SNF complex found mutated in cancer. More recently, at least seven other genes encoding SWI/SNF subunits have been identified as recurrently mutated in cancer. Collectively, 20% of all human cancers contain a SWI/SNF mutation. Consequently, investigation of the mechanisms by which SMARCB1 mutation causes cancer has relevance not only for rhabdoid tumors, but also potentially for the wide variety of SWI/SNF mutant cancers. Here we discuss normal functions of SMARCB1 and the SWI/SNF complex as well as mechanistic and potentially therapeutic insights that have emerged.

Keywords

Rhabdoid tumor; SMARCB1; Chromatin-remodeling complex; SWI/SNF; SNF5

Eukaryotes carry genetic information in a highly compacted organizational structure termed chromatin. The basic unit of chromatin consists of DNA wrapped around histones, collectively termed nucleosomes. Nucleosomes undergo progressive coiling to generate compact higher order structures. In order for cells to carry out processes such as

© 2014 Elsevier Inc. All rights reserved.

Conflict of Interest Statement: CWMR receives research support and consulting fees from the Novartis Institute for Biomedical Research (NIBR) via the Dana-Farber Cancer Institute-NIBR Drug Discovery Program. Novartis is the sponsor of the CDK4 inhibition trial cited above. CWMR has no role in this trial.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

transcriptional regulation, DNA repair, and DNA replication, chromatin and nucleosomal structures must be remodeled to generate accessible DNA. Three mechanisms involved in this process are covalent histone modification, incorporation of histone variants, and energy dependent remodeling of chromatin structure. With respect to the last category, there are at least five families of chromatin remodeling complexes; SWI/SNF, ISI, NuRD/Mi-2/CHD, INO80, and SWR1. Of these, the SWI/SNF complex, which is evolutionarily conserved from yeast to humans, represents a novel link between ATP-dependent chromatin remodeling and tumor suppression. The complex consists of 10–15 subunits, including core subunits present in all variants of the complex, SMARCB1 (SNF5), SMARCC1 (BAF155), SMARCC2 (BAF170), and two mutually exclusive ATPase subunits, SMARCA4 (also known as BRG1) or SMARCA2 (also known as BRM). Additionally, the complex contains a number of related lineage-restricted subunits that vary by cell type (1). For example the BAF45 subunit is encoded by four different, but highly related genes, *BAF45A*, *BAF45B*, *BAF45C*, and *BAF45D*. Similarly, the BAF60 (SMARCD) subunit is encoded by three different genes and the BAF53 (ACTL6) by two genes. In addition, groups of subunits can be exchanged for others. For instance, BAF variants of the complex can contain ARID1A or ARID1B, while in the PBAF variants of the complex these are replaced by ARID2 (BAF200), PBRM1 (BAF180), and BRD7. Consequently, while core remodeling complex subunits are ubiquitous, up to several hundred variants of the complex have been proposed that may contribute in a highly specific way to the regulation of lineage identity (2–5).

Nomenclature

First, a word on the complex, and at times confusing, nomenclature for the gene mutated in rhabdoid tumor. Four different names are in use for this gene, with use of the name varying by field of investigation. Those who came to know of the gene as a consequence of its original discovery in yeast often use the name “*SNF5*”, a reference to its discovery in a screen for genes required to metabolize sucrose. Such genes were called “Sucrose Non-Fermenting” or *SNF* genes. Those who discovered and learned of the human homolog from its interaction with the integrase of HIV typically refer to the gene as Integrase Interactor 1, or INI1. This latter name has often been in the human pathology and rhabdoid tumor literature. Separate from these two, the gene has been given an official HUGO name of SWI/SNF related, matrix associate, actin dependent regulator of Chromatin, Subfamily B, Member 1 (*SMARCB1*). Since *SMARCB1* is the “official” name, it has often been used in the cancer genome sequencing literature when lists of mutated genes are reported. Further, as the name has some official sanction, there has been some movement toward it. However, others prefer alternate nomenclature and refer to subunits of the complex as Brg1 associated factors (BAFs) followed by the mass of the protein in kilodaltons, thus resulting in related names for each subunit. The gene mutated in rhabdoid tumors is then referred to as *BAF47*. Thus far a consensus on terminology has yet to emerge. Hopefully, in the future, investigators from all of these fields can reach consensus on the nomenclature agreement. For the purposes of this review, we have chosen to use HUGO nomenclature but have previously, and recently, used other variations as well.

Rhabdoid tumors: linking SWI/SNF chromatin remodeling complexes to cancer

SMARCB1 (SNF5) is a core subunit present in all variants of the SWI/SNF complex. The first link between SMARCB1 and oncogenesis emerged from the study of rhabdoid tumors. Two laboratories discovered that specific, biallelic, inactivating mutations in *SMARCB1* are found in rhabdoid tumors (RTs) (6, 7), and further that heterozygous *Smarchb1* mutations are the basis of a familial cancer syndrome (7, 8). As described in more detail elsewhere in this issue, these cancers are aggressive and highly lethal pediatric tumors commonly found in the kidney, the central nervous system, where it is also known as atypical teratoid/rhabdoid tumor (AT/RT), and also less frequently in other soft tissues. Despite the use of intensive chemotherapy and radiotherapy, outcomes remain poor.

Recent data emerging from whole-exome sequencing of human cancers demonstrates that SMARCB1 is not the only subunit of the SWI/SNF complex mutated in cancer. Indeed, at least six genes encoding SWI/SNF subunits, including *ARID1A*, *ARID1B*, *ARID2*, *SMARCA4 (BRG1)*, *SMARCB1 (SNF5)*, *PBRM1*, and others, have been identified as recurrently mutated in wide spectrum of cancers (4) including ovarian (9, 10), lung (11, 12), liver (13, 14), pancreas (15), breast (16, 17), bladder (18), kidney (19), endometrial (20–22), skin (23), and brain cancers (24, 25), among others (26, 27) (Figure 1). As multiple SWI/SNF subunits are recurrently mutated in cancer, this suggests at least some degree of a shared mechanism of oncogenesis for these cancers. Consequently, findings and therapeutic insights from the study of the role of *SMARCB1* mutations in RT may have implications for the variety of other SWI/SNF mutant cancers.

SMARCB1 as a tumor suppressor: protecting the genome or epigenome?

Study of genetically engineered mouse models has demonstrated that homozygous *Smarchb1* deficiency results in early embryonic lethality while heterozygous mice are predisposed to aggressive cancers that are histologically quite similar to human RT, including the presence of classic rhabdoid cells (28–30). In the mice, as in humans, these tumors are aggressive, locally invasive, and frequently metastatic to regional lymph nodes and/or lung. In contrast, the location of *Smarchb1* deficient cancers in mice differs somewhat from those seen in humans. In mice, the tumors occur most commonly on the face and occasionally in brain, but never in kidney. Conditional, biallelic inactivation of *Smarchb1* using the interferon inducible Mx1-Cre transgene results in profound cancer predisposition. All of these mice develop aggressive cancer including mature T cell lymphomas and rhabdoid-like tumors at a median onset of only 11 weeks (31). This is quite rapid compared to other tumor suppressors. For example, *p53* inactivation leads to cancer at 20 weeks, *p19Arf* loss at 38 weeks, and *p16Ink4a* loss at 60 weeks. Thus, the rapid onset and complete penetrance of cancer following inactivation of *Smarchb1* established this gene as a potent and bona fide tumor suppressor.

SMARCB1 and the SWI/SNF complex have been implicated in several forms of DNA repair including DNA double-strand break repair (32), UV-induced DNA damage repair (33), homologous recombinational repair (34), DNA decatenation (35), and nucleotide

excision repair (36). Given this and the rapidity and full penetrance by which *Smarchb1* loss causes cancer, we and others initially hypothesized that *SMARCB1* loss drives cancer by leading to the rapid accumulation of DNA mutations and/or chromosomal instability. However, when testing this hypothesis we failed to detect major effects of *SMARCB1* loss upon DNA repair and found that RT were diploid and largely lacked gene amplifications or deletions detectable at the level of SNP arrays aside from deletions at the *SMARCB1* locus. Subsequently, via exome sequencing of RT we and others found that these cancers have a remarkably low rate of mutation (37–40) with loss of *SMARCB1* being essentially the sole recurrent event detected. Given the absence of genomic instability despite the rapidity by which *SMARCB1* deficient cancers arise both in humans and mice, these findings collectively suggest that the initiation and progression of aggressive cancers caused by *SMARCB1* loss may not arise due to effects upon genome integrity, but rather epigenetically via perturbation of transcriptional regulation.

It is worthy of note that the function of *SMARCB1* within the SWI/SNF complex remains largely unknown. *SMARCB1* contains no obvious domains that clearly indicate function, but does contain two imperfect repeats to which most protein-protein interactions map (41) and has been implicated in non-specific DNA binding. It has been reported dispensable for formation of the SWI/SNF complex (42) but implicated in contributing to the targeting of the SWI/SNF complex to promoters (43).

Pathways & mechanisms

Since the identification of *SMARCB1* mutations in RT, substantial efforts have sought to identify pathways and mechanisms (summarized in Figure 2) that underlie tumor formation. As many of these efforts are covered elsewhere in this issue, here we principally highlight a few findings to which we have contributed, at least in part.

SMARCB1 regulates Cyclin D1/CDK4 activation

In a search for genes and pathways regulated by *SMARCB1*, it was found that reintroduction of *SMARCB1* into an RT cell line resulted in G0–G1 cell cycle arrest associated with transcriptional repression of *Cyclin D1*, induction of *P16(INK4A)*, and hypophosphorylation of RB (44, 45). Cyclin D1 is overexpressed in many human tumors and plays important roles during cell cycle. It interacts with cyclin-dependent kinase (cdk) 4/6 facilitating the phosphorylation and inactivation of RB to mediate G₁ to S progression. It also regulates activity of several transcription factors in a cdk-independent manner. Subsequently, re-expression of *SMARCB1* was found to repress *Cyclin D1* transcription by directly recruiting HDAC activity to the *Cyclin D1* promoter (44–46). The requirement of Cyclin D1 for the genesis of rhabdoid tumors was then established *in vivo* when it was shown that genetic ablation of *Cyclin D1* blocked formation of rhabdoid tumors (47). In collaboration with others, we found that levels of the *Cyclin D1* transcript were high in ATRT compared to medulloblastomas or normal cerebellum. Notably, however, later studies of both renal rhabdoid tumors and ATRT did not detect elevated levels of *Cyclin D1* (48, 49). As described in greater detail elsewhere in this issue, efforts are now focused on determining whether RT are sensitive to pharmacological disruption of Cyclin D1/CDK4

(50), and a phase I clinical trial is now being conducted to test the response of RT patients to CDK4 inhibition (<http://clinicaltrials.gov/show/NCT01747876>).

SMARCB1 loss activates the Sonic Hedgehog pathway

The Hedgehog (Hh) pathway plays important roles modulating patterning and differentiation during development. A clear genetic contribution of Hh pathway activity to oncogenesis was first realized when loss-of function mutations in the Hh pathway in familial and sporadic basal cell carcinoma (mutations in the *PTCH1* gene), and medulloblastoma (mutations in the *SMO* gene) were identified (51, 52). Downstream, activation of glioma-associated oncogene homolog (GLI) transcription factors leads to transcription of Hh pathway target genes, including *GLI1*, *GLI2*, and *PTCH1*, and amplifications in the *GLI1* transcription factor also occurs in gliomas and medulloblastomas. A role for SMARCB1 and the SWI/SNF complex in the control of Hh signaling was studied when SMARCB1 was identified as one of the top interactors of *GLI1* and when human ATRT were found to have transcriptional profiles with similarities to Hh mutant medulloblastomas (53). Findings from this study demonstrated that SMARCB1 is directly recruited to the upstream regions of the transcription start sites of *GLI1* target genes, *GLI1* and *PTCH1*, and the expression of these genes were upregulated followed by shRNA-mediated knockdown of *SMARCB1*, supporting *GLI1* and *PTCH1* as direct targets. Conversely, re-expression of SMARCB1 in RT cells reduced *GLI1* expression substantially, revealing a novel function of SMARCB1 as a mediator of Hh signaling. Notably, inactivation of SMARCB1 was found to result in direct activation of *GLI1* mediated transcription and upstream inhibitors of the pathway, such as via inhibition of Smoothened (*SMO*), had no effect on expression of *GLI1* targets in SMARCB1-deficient RT cell lines.

SMARCB1 loss activates the WNT/ β -Catenin Pathway

Numerous studies have implicated the SWI/SNF complex in the control of lineage specification. For example, variations in the composition of SWI/SNF complexes have been shown to regulate transition from neural stem cell to post-mitotic neuron (3). Similarly, SMARCB1 is essential for hepatocyte differentiation (54) and likely for many other tissues as well (31). In mouse models, *Smarca4* and *Smarb1* knockout mice fail to develop past the blastocyst stage and in lineage specific experiments, SMARCA4 and SMARCB1 are essential for control of T-cell development (55). Additionally, SWI/SNF complexes have been shown required for proper development of blood, liver, heart, muscle, melanocyte, adipocyte, and bone lineages (56–59), suggesting a role for the complex in regulation of developmental pathways.

Canonical Wnt signaling (β -Catenin dependent) regulates genes that are involved in diverse cellular functions such as differentiation and proliferation and aberrant activation of Wnt signaling is found in several types of human cancer. Studies have implicated the SWI/SNF complex in regulation of the Wnt signaling pathway. For instance, SMARCA4 can directly modulate transcription of multiple Fzd receptors and a subset of Wnt target genes in yolk sac endothelial cells (YSECs) (60). Also, *SMARCB1* loss causes aberrant activation of the Wnt

pathway and results in phenotypic defects consistent with Wnt/ β -Catenin overexpression (61).

In addition, studies have implicated SMARCB1 in regulating numerous cancer-related genes, several of which we mention here. SMARCB1 has been implicated in the regulation of the cell cycle through RB-mediated repression of E2F target genes including *Cyclin A*, *E2F1*, and *CDC6* (62, 63) and in both SMARCB1-deficient RTs and *Smarb1*-deficient mouse embryonic fibroblasts, the expression of E2F target genes was increased (45, 64). In addition, several studies found either interactions of SMARCB1 with c-MYC and/or a role for SMARCB1 in the control of expression of both c-MYC and its targets (65, 66). Given that MYC is highly expressed in RTs (48, 67), the aberrant expression of MYC and its target genes may have a role in the growth of these cancers. SMARCB1 has also been implicated in the control of *P16(INK4A)* and both *in vitro* and *in vivo* data suggest that *P16(INK4A)* is a direct downstream target of SMARCB1 (44, 64, 68, 69). Additional downstream targets that may play a role in oncogenesis include Polo-like kinase1 (PLK1), Aurora A kinase (70), RhoA mediated control of migration (71).

Collectively, these and other findings have implicated subunits of the SWI/SNF complex in the transcriptional regulation of the cell cycle, development, proliferation, and differentiation. Interestingly, upon mutation of the complex, alteration in the activity of these pathways seems to occur directly at the level of chromatin. For example, activation of both the Hh and WNT pathways in the absence of SMARCB1 is not dependent upon activation of the canonical pathways. Indeed, upstream blockade of the Hh pathway via inhibition of Smoothened (SMO) had no effect upon the high level of pathway activity in the absence of SMARCB1 (53). Similarly, blockade of the upstream WNT pathway had no effect upon the high level expression of pathway targets (61). Collectively, these findings suggest that mutation of *SMARCB1* leads to alterations in chromatin structure that result in direct change to transcription and uncoupling of pathways from upstream canonical control.

Epigenetic antagonism between Polycomb and SWI/SNF complex during oncogenic transformation

So, how might changes in chromatin structure disrupt lineage specification? Enhancer of Zeste 2 (EZH2) is a histone-lysine N-methyltransferase that is the catalytic subunit of the Polycomb complex 2 (PRC2). It mediates the trimethylation of lysine 27 of histone H3 (H3K27me3), a repressive chromatin mark, playing a vital role in epigenetic gene silencing and oncogenic transformation. EZH2 has also been implicated in the regulation of pluripotency, differentiation, and proliferation (72, 73). Importantly, its deletion is embryonic lethal, suggesting that EZH2 is critical for normal development (74). Recently, EZH2 has been found to be over-expressed in numerous cancer types and associated with tumor cell proliferation, invasive growth, and poor prognosis (75, 76). Given that EZH2 has been implicated in development and maintenance of cancers, the mechanism of action of EZH2 has been evaluated in several malignancies. For instance, recent studies have demonstrated that disruption of aberrant EZH2 activity inhibited prostate cancer tumorigenicity (77) and EZH2 serves a crucial role for tumor stem cell maintenance in glioblastoma (78). Interestingly, the roles of EZH2 in oncogenesis may be highly context

dependent. For instance, gain-of-function somatic mutations of EZH2 have been found in B-cell non-Hodgkin's lymphoma while inactivating mutations of EZH2 occur in myelodysplastic syndrome (79–81). Thus appropriate control of EZH2 is important for normal development such that both over- and under-expression may be capable of promoting transformation in certain contexts.

Potential links between Polycomb and the SWI/SNF complex first emerged from genetic studies in *Drosophila*, from which mutations in SWI/SNF subunits were found act as positive regulators of *Hox* genes and to partially suppress the effects of Polycomb mutations (82). Proteins encoded by trithorax group genes activate expression of *Hox* genes while proteins encoded by polycomb genes mediate repression. Several members of the trithorax group of genes were subsequently found to encode subunits of the SWI/SNF complex including *Brm*, *moira* (BAF155 ortholog) and *Osa* (BAF270 ortholog). Mechanistic insight revealing that polycomb proteins can directly repress chromatin remodeling by SWI/SNF complexes was shown *in vitro* (83). This balance between Polycomb and SWI/SNF activity was found to extend to mammals and to be essential for tumor suppression by SMARCB1 as inactivation of the polycomb gene *Ezh2* using a conditional mouse model completely blocked tumor formation caused by *Smarchb1* inactivation (63). Mechanistically, deletion of SMARCB1 led to elevated expression and recruitment of EZH2 to Polycomb targets that became broadly H3K27-trimethylated and repressed in SMARCB1-deficient fibroblasts and cancers. Importantly, these effects were highly specific, as knockout of EZH2 completely blocked the growth of *SMARCB1* mutant cancers, but had no effect on osteosarcomas driven by *p53/Rb* loss. In follow up to this work, a small molecule inhibitors (EPZ-6438), which block the methyltransferase active site of EZH2 was shown to specifically inhibit cellular H3K27 methylation and selectively induce apoptotic death of *SMARCB1* mutant RT cells both in culture and in xenograft experiments *in vivo* (84). Consequently, there is interest in testing EZH2 inhibitors in patients who have recurrent/progressive RT, as such disease is nearly uniformly fatal.

The Swi/Snf complex contributes to transcriptional regulation by mobilizing nucleosomes

Appropriate regulation of gene expression requires the interplay of complexes that modulate chromatin compaction in conjunction with sequence-specific transcription factors and basal transcription machinery. Nucleosome occupancy and position correlate with transcription rate as, for example, gene activation correlates with additional nucleosome depletion (85, 86). In addition, the promoter regions of active genes are enriched with nucleosomes containing specific post-translationally modified histones that carry correlate with modulation of transcription rate.

The role of the SWI/SNF complex in cell fate specification has been postulated to arise in large part from nucleosome mobilization driven by the activity of its ATPase subunits (SMARCA4 and SMARCA2). The molecular mechanism by which the SWI/SNF complex alters chromatin structure has been an active area of investigation. Evidence supports a role for the SWI/SNF complex in controlling nucleosome position and transcription regulation. For instance, it has been reported that purified SWI/SNF complex is able to mobilize

chromatinized nucleosomes *in vitro* and the complex can bind preferentially to promoters and other regulatory regions to move nucleosomes *in vivo* (87–91).

Recent studies have used murine embryonic fibroblasts (MEFs) to demonstrate perturbation in SWI/SNF-driven regulation of chromatin structure and transcription when core subunits, *Smarchb1* or *Smarca4*, are conditionally knocked out. In this study, the function of each subunit and its contribution to chromatin structure alteration were directly compared on a uniform genetic background. The analysis showed that *Smarchb1* and *Smarca4* are essential for the establishment of appropriate nucleosome structures surrounding transcription start sites (TSS) genome wide (92). The complex may also serve roles in the regulation of enhancers (93, 94). Despite marked alterations in nucleosome occupancy, *Smarchb1* and *Smarca4* deficient MEFs did not have large differences in gene expression levels when compared to wild-type MEFs. These findings were perhaps surprising given previous findings that open promoter states are established when they are activated. However, the relationship between nucleosome occupancy and gene expression is complex as it has been demonstrated that even promoters of infrequently transcribed genes can stably form open states and nucleosome depletion is not sufficient to induce transcription activation (95, 96). In addition, there are more factors to consider at promoters, such as histone modifications, histone variants, and proteins that can modify post-translational modification of histone tails, not to mention at distal enhancers, in order to fully understand how nucleosome position contributes to transcriptional regulation. Consequently, nucleosome occupancy can affect both activation and repression of genes and there is a great need for further study of the contributions of SWI/SNF mediated nucleosome regulation to transcriptional regulation.

Conclusion

Rhabdoid tumors are rare cancers that strike young children and result in poor survival rates. *SMARCB1* is mutated in the vast majority of RT, cancers that otherwise have remarkably simple genomes. Although mutation of *SMARCB1* was the first SWI/SNF subunit mutation identified in human cancers, recent findings from cancer genome sequencing studies show that other SWI/SNF subunits are also mutated at a high frequency in a variety of human cancers (Fig 1).

Cancer is largely thought to be a disease dependent upon aberrant expression of genes involved in key cellular pathways that regulate proliferation, survival, and apoptosis. Recent cancer genome sequencing data have identified frequent mutations of genes that are involved in regulation of chromatin structure, with mutations in subunits of the SWI/SNF complex perhaps being the most frequent. These discoveries highlight the important interrelationships between genetic and epigenetic changes in the genesis of cancer. However, the specific mechanisms by which mutation of chromatin regulators drive cancer remain largely unclear.

Although it has been established that the *SMARCB1* and the SWI/SNF complex contribute to regulation of some canonical cancer-related pathways, given that the complex binds to the promoters of roughly one-third of all genes, as well as to active enhancers, the fundamental mechanisms tumor suppression seem unlikely to be derived from a single downstream target

pathway but more likely the result of disruption of coordinated pathways of lineage specific signaling. Consequently, pursuit of further insight into the fundamental role of the SWI/SNF complex in transcription regulation should help to understand the role of SMARCB1 and the SWI/SNF complex in tumor suppression. Given the simple genomes of RT and the rapidity with which cancer forms in Smarcb1 mutant mice, study of SMARCB1 offers potential benefit not only to patients with RT but can serve as a useful model with which to potentially identify therapeutic vulnerabilities conferred by SWI/SNF mutation across the wide variety of SWI/SNF mutant cancers.

Acknowledgments

This work and our efforts described herein were supported in part by R01CA113794 and R01CA172152 (to CWMR); and Alex's Lemonade Stand Innovation and Hyundai Hope on Wheels Awards (CWMR). The Garrett B. Smith Foundation, Miles for Mary, Cure AT/RT Now, and the Avalanna Fund (CWMR) provided additional support. KHK was supported by an award from National Cancer Center.

References

1. Nie Z, Xue Y, Yang D, et al. A specificity and targeting subunit of a human SWI/SNF family-related chromatin-remodeling complex. *Molecular and cellular biology*. 2000; 20:8879–88. [PubMed: 11073988]
2. Hargreaves DC, Crabtree GR. ATP-dependent chromatin remodeling: genetics, genomics and mechanisms. *Cell Res*;. 21:396–420.
3. Lessard J, Wu JI, Ranish JA, et al. An essential switch in subunit composition of a chromatin remodeling complex during neural development. *Neuron*. 2007; 55:201–15. [PubMed: 17640523]
4. Wilson BG, Roberts CW. SWI/SNF nucleosome remodellers and cancer. *Nat Rev Cancer*. 2011; 11:481–92. [PubMed: 21654818]
5. Wang W, Cote J, Xue Y, et al. Purification and biochemical heterogeneity of the mammalian SWI-SNF complex. *EMBO Journal*. 1996; 15:5370–82. [PubMed: 8895581]
6. Versteeg I, Sevenet N, Lange J, et al. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature*. 1998; 394:203–6. [PubMed: 9671307]
7. Biegel JA, Zhou JY, Rorke LB, et al. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. *Cancer Res*. 1999; 59:74–9. [PubMed: 9892189]
8. Sevenet N, Sheridan E, Amram D, et al. Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. *American journal of human genetics*. 1999; 65:1342–8. [PubMed: 10521299]
9. Jones S, Wang TL, Shih Ie M, et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. *Science*;. 330:228–31.
10. Wiegand KC, Shah SP, Al-Agha OM, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med*;. 363:1532–43.
11. Reisman DN, Sciarrotta J, Wang W, et al. Loss of BRG1/BRM in human lung cancer cell lines and primary lung cancers: correlation with poor prognosis. *Cancer Res*. 2003; 63:560–6. [PubMed: 12566296]
12. Medina PP, Romero OA, Kohno T, et al. Frequent BRG1/SMARCA4-inactivating mutations in human lung cancer cell lines. *Hum Mutat*. 2008; 29:617–22. [PubMed: 18386774]
13. Fujimoto A, Totoki Y, Abe T, et al. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. *Nat Genet*;. 44:760–4.
14. Li M, Zhao H, Zhang X, et al. Inactivating mutations of the chromatin remodeling gene ARID2 in hepatocellular carcinoma. *Nat Genet*;. 43:828–9.

15. Shain AH, Giacomini CP, Matsukuma K, et al. Convergent structural alterations define SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeler as a central tumor suppressive complex in pancreatic cancer. *Proc Natl Acad Sci U S A*. 109:E252–9. [PubMed: 22233809]
16. Xia W, Nagase S, Montia AG, et al. BAF180 is a critical regulator of p21 induction and a tumor suppressor mutated in breast cancer. *Cancer Res*. 2008; 68:1667–74. [PubMed: 18339845]
17. Stephens PJ, Tarpey PS, Davies H, et al. The landscape of cancer genes and mutational processes in breast cancer. *Nature*;. 486:400–4.
18. Gui Y, Guo G, Huang Y, et al. Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder. *Nat Genet*;. 43:875–8.
19. Varela I, Tarpey P, Raine K, et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. *Nature*;. 469:539–42.
20. Fadare O, Renshaw IL, Liang SX. Does the Loss of ARID1A (BAF-250a) Expression in Endometrial Clear Cell Carcinomas Have Any Clinicopathologic Significance?. A Pilot Assessment. *J Cancer*;. 3:129–36.
21. Samartzis EP, Noske A, Dedes KJ, et al. ARID1A mutations and PI3K/AKT pathway alterations in endometriosis and endometriosis-associated ovarian carcinomas. *Int J Mol Sci*;. 14:18824–49.
22. Bosse T, ter Haar NT, Seeber LM, et al. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations, TP53 and microsatellite instability in endometrial cancer. *Mod Pathol*;. 26:1525–35.
23. Lin H, Wong RP, Martinka M, et al. Loss of SNF5 expression correlates with poor patient survival in melanoma. *Clin Cancer Res*. 2009; 15:6404–11. [PubMed: 19808872]
24. Parsons DW, Li M, Zhang X, et al. The genetic landscape of the childhood cancer medulloblastoma. *Science*;. 331:435–9.
25. Robinson G, Parker M, Kranenburg TA, et al. Novel mutations target distinct subgroups of medulloblastoma. *Nature*;. 488:43–8.
26. Sausen M, Leary RJ, Jones S, et al. Integrated genomic analyses identify ARID1A and ARID1B alterations in the childhood cancer neuroblastoma. *Nature Genetics*;. 45:12–7.
27. Love C, Sun Z, Jima D, et al. The genetic landscape of mutations in Burkitt lymphoma. *Nat Genet*;. 44:1321–5.
28. Roberts CW, Galusha SA, McMenamin ME, et al. Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2000; 97:13796–800. [PubMed: 11095756]
29. Klochendler-Yeivin A, Fiette L, Barra J, et al. The murine SNF5/INI1 chromatin remodeling factor is essential for embryonic development and tumor suppression. *EMBO reports*. 2000; 1:500–6. [PubMed: 11263494]
30. Guidi CJ, Sands AT, Zambrowicz BP, et al. Disruption of Ini1 leads to peri-implantation lethality and tumorigenesis in mice. *Molecular and cellular biology*. 2001; 21:3598–603. [PubMed: 11313485]
31. Roberts CW, Leroux MM, Fleming MD, et al. Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene Snf5. *Cancer Cell*. 2002; 2:415–25. [PubMed: 12450796]
32. Chai B, Huang J, Cairns BR, et al. Distinct roles for the RSC and Swi/Snf ATP-dependent chromatin remodelers in DNA double-strand break repair. *Genes and Development*. 2005; 19:1656–61. [PubMed: 16024655]
33. Zhang L, Chen H, Gong M, et al. The chromatin remodeling protein BRG1 modulates BRCA1 response to UV irradiation by regulating ATR/ATM activation. *Frontiers in oncology*. 2013; 3:7. [PubMed: 23346553]
34. Sinha M, Watanabe S, Johnson A, et al. Recombinational repair within heterochromatin requires ATP-dependent chromatin remodeling. *Cell*. 2009; 138:1109–21. [PubMed: 19766565]
35. Dykhuizen EC, Hargreaves DC, Miller EL, et al. BAF complexes facilitate decatenation of DNA by topoisomerase IIalpha. *Nature*;. 497:624–7.
36. Hara R, Mo J, Sancar A. DNA damage in the nucleosome core is refractory to repair by human excision nuclease. *Mol Cell Biol*. 2000; 20:9173–81. [PubMed: 11094069]

37. Lee RS, Stewart C, Carter SL, et al. A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. *Journal of Clinical Investigation*; 122:2983–8.
38. Chakravadhanula M, Tembe W, Legendre C, et al. Detection of an Atypical Teratoid Rhabdoid Brain Tumor Gene Deletion in Circulating Blood Using Next-Generation Sequencing. *J Child Neurol*.
39. Hasselblatt M, Isken S, Linge A, et al. High-resolution genomic analysis suggests the absence of recurrent genomic alterations other than SMARCB1 aberrations in atypical teratoid/rhabdoid tumors. *Genes Chromosomes Cancer*; 52:185–90.
40. Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature*; 499:214–8.
41. Cheng SW, Davies KP, Yung E, et al. c-MYC interacts with INI1/hSNF5 and requires the SWI/SNF complex for transactivation function. *Nat Genet*. 1999; 22:102–5. [PubMed: 10319872]
42. Doan DN, Veal TM, Yan Z, et al. Loss of the INI1 tumor suppressor does not impair the expression of multiple BRG1-dependent genes or the assembly of SWI/SNF enzymes. *Oncogene*. 2004; 23:3462–73. [PubMed: 14990991]
43. Kuwahara Y, Wei D, Durand J, et al. SNF5 reexpression in malignant rhabdoid tumors regulates transcription of target genes by recruitment of SWI/SNF complexes and RNAPII to the transcription start site of their promoters. *Mol Cancer Res*; 11:251–60.
44. Betz BL, Strobeck MW, Reisman DN, et al. Re-expression of hSNF5/INI1/BAF47 in pediatric tumor cells leads to G1 arrest associated with induction of p16ink4a and activation of RB. *Oncogene*. 2002; 21:5193–203. [PubMed: 12149641]
45. Versteeg I, Medjkan S, Rouillard D, et al. A key role of the hSNF5/INI1 tumour suppressor in the control of the G1-S transition of the cell cycle. *Oncogene*. 2002; 21:6403–12. [PubMed: 12226744]
46. Zhang ZK, Davies KP, Allen J, et al. Cell cycle arrest and repression of cyclin D1 transcription by INI1/hSNF5. *Mol Cell Biol*. 2002; 22:5975–88. [PubMed: 12138206]
47. Tsikitis M, Zhang Z, Edelman W, et al. Genetic ablation of Cyclin D1 abrogates genesis of rhabdoid tumors resulting from Ini1 loss. *Proc Natl Acad Sci U S A*. 2005; 102:12129–34. [PubMed: 16099835]
48. Gadd S, Sredni ST, Huang CC, et al. Rhabdoid tumor: gene expression clues to pathogenesis and potential therapeutic targets. *Lab Invest*; 90:724–38.
49. Judkins AR, Mauger J, Ht A, et al. Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. *American Journal of Surgical Pathology*. 2004; 28:644–50. [PubMed: 15105654]
50. Alarcon-Vargas D, Zhang Z, Agarwal B, et al. Targeting cyclin D1, a downstream effector of INI1/hSNF5, in rhabdoid tumors. *Oncogene*. 2006; 25:722–34. [PubMed: 16302003]
51. Gailani MR, Stahle-Backdahl M, Leffell DJ, et al. The role of the human homologue of *Drosophila* patched in sporadic basal cell carcinomas. *Nat Genet*. 1996; 14:78–81. [PubMed: 8782823]
52. Raffel C, Jenkins RB, Frederick L, et al. Sporadic medulloblastomas contain PTCH mutations. *Cancer Res*. 1997; 57:842–5. [PubMed: 9041183]
53. Jagani Z, Mora-Blanco EL, Sansam CG, et al. Loss of the tumor suppressor Snf5 leads to aberrant activation of the Hedgehog-Gli pathway. *Nature Medicine*; 16:1429–33.
54. Gresh L, Bourachot B, Reimann A, et al. The SWI/SNF chromatin-remodeling complex subunit SNF5 is essential for hepatocyte differentiation. *EMBO J*. 2005; 24:3313–24. [PubMed: 16138077]
55. Chi TH, Wan M, Lee PP, et al. Sequential roles of Brg, the ATPase subunit of BAF chromatin remodeling complexes, in thymocyte development. *Immunity*. 2003; 19:169–82. [PubMed: 12932351]
56. Bultman SJ, Gebuhr TC, Magnuson T. A Brg1 mutation that uncouples ATPase activity from chromatin remodeling reveals an essential role for SWI/SNF-related complexes in beta-globin expression and erythroid development. *Genes Dev*. 2005; 19:2849–61. [PubMed: 16287714]
57. de la Serna IL, Carlson KA, Imbalzano AN. Mammalian SWI/SNF complexes promote MyoD-mediated muscle differentiation. *Nat Genet*. 2001; 27:187–90. [PubMed: 11175787]

58. Young DW, Pratap J, Javed A, et al. SWI/SNF chromatin remodeling complex is obligatory for BMP2-induced, Runx2-dependent skeletal gene expression that controls osteoblast differentiation. *J Cell Biochem.* 2005; 94:720–30. [PubMed: 15565649]
59. Pedersen TA, Kowenz-Leutz E, Leutz A, et al. Cooperation between C/EBPalpha TBP/TFIIB and SWI/SNF recruiting domains is required for adipocyte differentiation. *Genes Dev.* 2001; 15:3208–16. [PubMed: 11731483]
60. Griffin CT, Curtis CD, Davis RB, et al. The chromatin-remodeling enzyme BRG1 modulates vascular Wnt signaling at two levels. *Proc Natl Acad Sci U S A.* 108:2282–7.
61. Mora-Blanco EL, Mishina Y, Tillman EJ, et al. Activation of beta-catenin/TCF targets following loss of the tumor suppressor SNF5. *Oncogene.* 33:933–8.
62. Zhang HS, Gavin M, Dahiya A, et al. Exit from G1 and S phase of the cell cycle is regulated by repressor complexes containing HDAC-Rb-hSWI/SNF and Rb-hSWI/SNF. *Cell.* 2000; 101:79–89. [PubMed: 10778858]
63. Wilson BG, Wang X, Shen X, et al. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell.* 18:316–28.
64. Isakoff MS, Sansam CG, Tamayo P, et al. Inactivation of the Snf5 tumor suppressor stimulates cell cycle progression and cooperates with p53 loss in oncogenic transformation. *Proc Natl Acad Sci U S A.* 2005; 102:17745–50. [PubMed: 16301525]
65. Khavari PA, Peterson CL, Tamkun JW, et al. BRG1 contains a conserved domain of the SWI2/SNF2 family necessary for normal mitotic growth and transcription. *Nature.* 1993; 366:170–4. [PubMed: 8232556]
66. Wang X, Werneck MB, Wilson BG, et al. TCR-dependent transformation of mature memory phenotype T cells in mice. *J Clin Invest.* 121:3834–45.
67. McKenna ES, Sansam CG, Cho YJ, et al. Loss of the epigenetic tumor suppressor SNF5 leads to cancer without genomic instability. *Mol Cell Biol.* 2008; 28:6223–33. [PubMed: 18710953]
68. Chai J, Charboneau AL, Betz BL, et al. Loss of the hSNF5 gene concomitantly inactivates p21CIP/WAF1 and p16INK4a activity associated with replicative senescence in A204 rhabdoid tumor cells. *Cancer Res.* 2005; 65:10192–8. [PubMed: 16288006]
69. Oruetebarria I, Venturini F, Kekarainen T, et al. P16INK4a is required for hSNF5 chromatin remodeler-induced cellular senescence in malignant rhabdoid tumor cells. *J Biol Chem.* 2004; 279:3807–16. [PubMed: 14604992]
70. Lee S, Cimica V, Ramachandra N, et al. Aurora A is a repressed effector target of the chromatin remodeling protein INI1/hSNF5 required for rhabdoid tumor cell survival. *Cancer Res.* 71:3225–35.
71. Caramel J, Quignon F, Delattre O. RhoA-dependent regulation of cell migration by the tumor suppressor hSNF5/INI1. *Cancer Res.* 2008; 68:6154–61. [PubMed: 18676838]
72. Cao R, Wang L, Wang H, et al. Role of histone H3 lysine 27 methylation in Polycomb-group silencing. *Science.* 2002; 298:1039–43. [PubMed: 12351676]
73. Margueron R, Reinberg D. The Polycomb complex PRC2 and its mark in life. *Nature.* 469:343–9.
74. O'Carroll D, Erhardt S, Pagani M, et al. The polycomb-group gene *Ezh2* is required for early mouse development. *Mol Cell Biol.* 2001; 21:4330–6. [PubMed: 11390661]
75. Zeidler M, Varambally S, Cao Q, et al. The Polycomb group protein EZH2 impairs DNA repair in breast epithelial cells. *Neoplasia.* 2005; 7:1011–9. [PubMed: 16331887]
76. Chang CJ, Hung MC. The role of EZH2 in tumour progression. *Br J Cancer.* 106:243–7.
77. Crea F, Hurt EM, Mathews LA, et al. Pharmacologic disruption of Polycomb Repressive Complex 2 inhibits tumorigenicity and tumor progression in prostate cancer. *Mol Cancer.* 10:40. [PubMed: 21501485]
78. Suva ML, Riggi N, Janiszewska M, et al. EZH2 is essential for glioblastoma cancer stem cell maintenance. *Cancer Res.* 2009; 69:9211–8. [PubMed: 19934320]
79. Morin RD, Johnson NA, Severson TM, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat Genet.* 42:181–5.
80. Beguelin W, Popovic R, Teater M, et al. EZH2 is required for germinal center formation and somatic EZH2 mutations promote lymphoid transformation. *Cancer Cell.* 23:677–92.

81. Nikoloski G, Langemeijer SM, Kuiper RP, et al. Somatic mutations of the histone methyltransferase gene EZH2 in myelodysplastic syndromes. *Nat Genet.*; 42:665–7.
82. Kennison JA. The Polycomb and trithorax group proteins of *Drosophila*: trans-regulators of homeotic gene function. *Annu Rev Genet.* 1995; 29:289–303. [PubMed: 8825476]
83. Shao Z, Raible F, Mollaaghababa R, et al. Stabilization of chromatin structure by PRC1, a Polycomb complex. *Cell.* 1999; 98:37–46. [PubMed: 10412979]
84. Knutson SK, Warholik NM, Wigle TJ, et al. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. *Proc Natl Acad Sci U S A.*; 110:7922–7.
85. Lee CK, Shibata Y, Rao B, et al. Evidence for nucleosome depletion at active regulatory regions genome-wide. *Nat Genet.* 2004; 36:900–5. [PubMed: 15247917]
86. Sekinger EA, Moqtaderi Z, Struhl K. Intrinsic histone-DNA interactions and low nucleosome density are important for preferential accessibility of promoter regions in yeast. *Mol Cell.* 2005; 18:735–48. [PubMed: 15949447]
87. Kwon H, Imbalzano AN, Khavari PA, et al. Nucleosome disruption and enhancement of activator binding by a human SWI/SNF complex. *Nature.* 1994; 370:477–81. [PubMed: 8047169]
88. Zofall M, Persinger J, Kassabov SR, et al. Chromatin remodeling by ISW2 and SWI/SNF requires DNA translocation inside the nucleosome. *Nature structural & molecular biology.* 2006; 13:339–46.
89. Sen P, Ghosh S, Pugh BF, et al. A new, highly conserved domain in Swi2/Snf2 is required for SWI/SNF remodeling. *Nucleic acids research.* 2011; 39:9155–66. [PubMed: 21835776]
90. Sims HI, Baughman CB, Schnitzler GR. Human SWI/SNF directs sequence-specific chromatin changes on promoter polynucleosomes. *Nucleic acids research.* 2008; 36:6118–31. [PubMed: 18820294]
91. Ulyanova NP, Schnitzler GR. Human SWI/SNF generates abundant, structurally altered dinucleosomes on polynucleosomal templates. *Molecular and cellular biology.* 2005; 25:11156–70. [PubMed: 16314535]
92. Tolstorukov MY, Sansam CG, Lu P, et al. Swi/Snf chromatin remodeling/tumor suppressor complex establishes nucleosome occupancy at target promoters. *Proceedings of the National Academy of Sciences of the United States of America.*; 110:10165–70.
93. Chi TH, Wan M, Zhao K, et al. Reciprocal regulation of CD4/CD8 expression by SWI/SNF-like BAF complexes. *Nature.* 2002; 418:195–9. [PubMed: 12110891]
94. Hu G, Schones DE, Cui K, et al. Regulation of nucleosome landscape and transcription factor targeting at tissue-specific enhancers by BRG1. *Genome Res.*; 21:1650–8.
95. Shivaswamy S, Bhinge A, Zhao Y, et al. Dynamic remodeling of individual nucleosomes across a eukaryotic genome in response to transcriptional perturbation. *PLoS Biol.* 2008; 6:e65. [PubMed: 18351804]
96. Jiang C, Pugh BF. Nucleosome positioning and gene regulation: advances through genomics. *Nat Rev Genet.* 2009; 10:161–72. [PubMed: 19204718]

Figure 1. The SWI/SNF ATPase subunit genes are frequently mutated in specific types of human cancers

The cancers in which genes encoding SWI/SNF subunits have been reported mutant.

Figure 2.
The SWI/SNF complex regulates expression of numerous target genes and pathways.