The Many Roles of BAF (mSWI/SNF) and PBAF Complexes in Cancer

Courtney Hodges, Jacob G. Kirkland, and Gerald R. Crabtree

Departments of Pathology, Developmental Biology, and Genetics, Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California 94305

Correspondence: crabtree@stanford.edu

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

During the last decade, a host of epigenetic mechanisms were found to contribute to cancer and other human diseases. Several genomic studies have revealed that ~20% of malignancies have alterations of the subunits of polymorphic BRG-/BRM-associated factor (BAF) and Polybromo-associated BAF (PBAF) complexes, making them among the most frequently mutated complexes in cancer. Recurrent mutations arise in genes encoding several BAF/PBAF subunits, including *ARID1A*, *ARID2*, *PBRM1*, *SMARCA4*, and *SMARCB1*. These subunits share some degree of conservation with subunits from related adenosine triphosphate (ATP)-dependent chromatin remodeling complexes in model organisms, in which a large body of work provides insight into their roles in cancer. Here, we review the roles of BAF- and PBAF-like complexes in these organisms, and relate these findings to recent discoveries in cancer epigenomics. We review several roles of BAF and PBAF complexes in cancer, including transcriptional regulation, DNA repair, and regulation of chromatin architecture and topology. More recent results highlight the need for new techniques to study these complexes.

EPIGENOMICS IN CANCER

Broadly defined, epigenetic factors contribute to the expression state of the genome by regulating heritable changes in gene expression independently of the DNA sequence. Chromatin-based epigenetic regulation occurs through a wide variety of mechanisms, including physical compaction and exclusion, recruitment of transcription machinery, or covalent modification of DNA and histones. Such features constitute the heritable physicochemical state of the genetic material, and are jointly referred to as the epigenetic landscape. The combinatorial regulation of these features represents the full spectrum of achievable cell-type diversity for the organism. Because epigenetic regulation contributes to cell-type functional specialization, it is essential for multicellular life.

An important component of the epigenetic state is the regulation provided by adenosine triphosphate (ATP)-dependent chromatin remodelers, which use ATP to physically remodel histones and other factors on chromatin. As we review below, genomic studies of primary tumors and cancer cell lines have revealed that ATP-dependent chromatin remodelers are among the most frequently disrupted genes in cancer. Because several important components of ATP-dependent chromatin remodelers

Editors: Scott A. Armstrong, Steven Henikoff, and Christopher R. Vakoc
Additional Perspectives on Chromatin Deregulation in Cancer available at www.perspectivesinmedicine.org

Advanced Online Article. Cite this article as *Cold Spring Harb Perspect Med* doi: 10.1101/cshperspect.a026930

are conserved between yeast, flies, and humans (Fig. 1), the basic research on chromatin remodeling performed in model organisms is taking on new relevance for disease biology. In many cases, fundamental observations from yeast and flies directly support our understanding of the role of chromatin remodelers in cancer; in other cases, the differences between these organisms and humans highlight important gaps in our knowledge of disease mechanisms.

In this review, we focus on the family of BRG-/BRM-associated factor ([BAF] or mSWI/SNF) and Polybromo-associated BAF (PBAF) complexes, whose subunits have been identified as major tumor suppressors in several malignancies (Davoli et al. 2013; Kadoch et al. 2013; Shain and Pollack 2013). Here, we relate the fundamental biology revealed by genetics, structural biology, and microscopy to the fast-moving field of cancer epigenomics. As we discuss below, the mechanisms revealed by fundamental studies inform our understanding of how epigenetic dysfunction contributes to cancer.

SWI/SNF AND RSC IN *Saccharomyces cerevisiae*

The SWI/SNF Complex

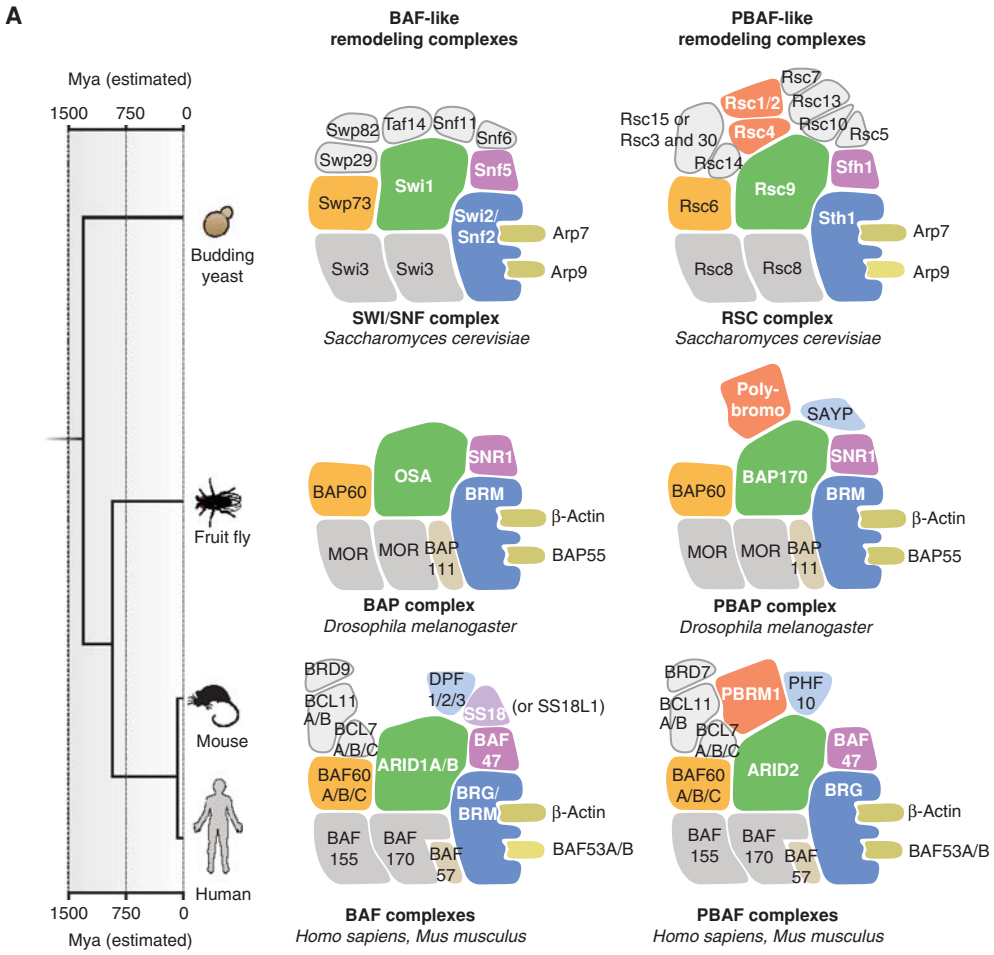
ATP-dependent chromatin remodelers were independently discovered in yeast, by screening for mutations that disrupt the ability of yeast to switch mating type (Stern et al. 1984) or activate sucrose fermentation pathways (Carlson et al. 1981; Neigeborn and Carlson 1984, 1987), both in response to extrinsic cues. Later work showed that many of these genes act in concert through a common complex that regulated transcription, termed SWI/SNF to honor both discoveries (Peterson and Herskowitz 1992; Winston and Carlson 1992; Cairns et al. 1994; Peterson et al. 1994). The observation that histone mutants were able to reverse the phenotypic defects associated with SWI/SNF mutation (Sternberg et al. 1987; Kruger et al. 1995) indicated that regulation of chromatin structure was the central function of the SWI/SNF complex. In vitro, ATP-dependent remodeling activity induces changes of position, phasing, stability, or histone content of nucleosomes, and is well described in other reviews (Becker and Horz 2002; Narlikar et al. 2013). However, as we discuss below, SWI/SNF-like complexes have rich and biologically diverse regulatory roles in vivo that arise through mechanisms that are not entirely clear.

In yeast, SWI/SNF is a ~1.15-MDa protein complex (Smith et al. 2003) composed of Swi1, Snf2, Swi3, Snf5, Snf6, along with Swp- and actin-related proteins (ARPs) (Fig. 1). Most subunits of the complex, including the ATPase Snf2, are present as single copies in the complex, whereas several others integrate in multiple copies (two copies of Swi3, Swp82, Snf6, and Snf11, and three copies of Swp29) (Smith et al. 2003). Many of these subunits are required for the complex's biological activity and, in some cases, its biochemical stability (Estruch and Carlson 1990; Richmond and Peterson 1996). The complex's direct interaction with nucleosomal DNA is mediated by the catalytic subunit Snf2, whereas other subunits, such as Snf5, do not interact with nucleosomal DNA but instead contact the histone octamer (Dechassa et al. 2008).

Cells with SWI/SNF subunit mutations have disrupted chromatin structures, and fail to express many genes, leading to diverse phenotypic defects. As a result, several aspects of the complex's biological activity are illustrated by genetic deletion of its subunits.

Failure to activate gene expression affects several downstream processes. As an example, cells lacking the central ATPase Snf2 are viable but have impaired mating-type switching because of the inability to express the HO endonuclease needed for the process. Proper expression of HO depends not only on Snf2, but also Snf1 and Swi3 (Stern et al. 1984). In addition to the effects on sucrose metabolism, *snf2*Δ cells also have impaired sporulation. However, SWI/SNF activity is not uniformly activating. Although Snf2 plays a role in activation of many genes, it also is required for silencing of genes at rDNA and telomeric loci, either by direct or indirect means (Dror and Winston 2004; Manning and Peterson 2014).

SWI/SNF subunits also have important functions in maintaining proper chromatin-



B

HUGO symbol	Alternative names	HUGO symbol	Alternative names
ACTL6A/B	BAF53A/B	**SMARCA2**	BRM
ARID1A/B	BAF250A/B	**SMARCA4**	BRG
ARID2	BAF200	**SMARCB1**	BAF47, SNF5, INI1
BCL7A/B/C	–	**SMARCC1/2**	BAF155/BAF170
BCL11A/B	–	**SMARCD1/2/3**	BAF60A/B/C
BRD7/9	–	**SMARCE1**	BAF57
DPF1/2/3	BAF45B/D/C	**SS18**	–
PBRM1	BAF180, Polybromo	**SS18L1**	CREST
PHF10	BAF45A		

Figure 1. Homology between BAF and PBAF-like remodelers throughout evolution. (*A*) BAF and PBAF complexes in mammals share several features with Brahma-associated proteins (BAPs) and Polybromo-associated BAP (PBAP) complexes (*Drosophila melanogaster*), and SWI/SNF and RSC complexes (*Saccharomyces cerevisiae*), respectively. The similarities and differences between these complexes throughout evolution provide insight into their biological regulation and their roles in cancer. BAF/PBAF subunits labeled in a boldface white font have important roles in malignancy. Time since species divergence was estimated using TimeTree (Hedges et al. 2006), and plotted as a function of time, millions of years ago (Mya). (*B*) Summary of BAF and PBAF subunits and alternative names used in the text. In some cases, abbreviated names rather than the official human genome organization (HUGO) symbols are used in the text because of space constraints.

modification domains. In a reporter strain that lacks a native transfer RNA (tRNA) insulator element, nucleosomes occupy a region from which they are normally depleted, leading to loss of insulator function (Oki et al. 2004). In this system, artificial recruitment of Snf5 or Snf6 restores the nucleosome-depleted region over which heterochromatin marks cannot spread, thereby rescuing barrier function.

SWI/SNF mutations also cause increased sensitivity to DNA-damaging agents, including hydroxyurea, cisplatin, methyl methanesulfonate, and ultraviolet (UV) light (Birrell et al. 2001; Chai et al. 2005; Xia et al. 2007). These defects may arise because SWI/SNF subunits have roles in nucleotide excision repair (Gong et al. 2006) and DNA double-strand break (DSB) repair through the homologous recombination (HR) pathway (Chai et al. 2005). SWI/SNF defective cells also show increased sensitivity to the topoisomerase II inhibitor daunorubicin (Xia et al. 2007).

Because transcription, DNA repair, and chromatin modification domains are each influenced by the availability of accessible DNA, disruption of the nucleosome mobilization activity of SWI/SNF has distinct and pleiotropic effects.

The RSC Complex

In budding yeast, *STH1* codes for the ATPase subunit of the RSC complex, which also has the capacity to remodel the structure of chromatin. In addition to Sth1, whose ATPase domain is functionally interchangeable with Snf2 (Laurent et al. 1993), the RSC complex also has Rsc4, Rsc6, Rsc8, Rsc9, Sfh1, and several other dedicated subunits (Fig. 1). In budding yeast, there are two distinct RSC complexes, containing either of the two paralogs Rsc1 or Rsc2 that arose from gene duplication. Both subunits along with Rsc4 contain bromodomains, which interact with acetylated lysines. RSC complexes are ~10-fold more abundant that SWI/SNF (Cairns et al. 1996, 1999), which may explain why RSC complexes are essential but SWI/SNF is not. Electron microscopic (EM) reconstructions of the yeast RSC complex show a lobed ~1.3-MDa structure of similar scale to the SWI/SNF complex (Asturias et al. 2002; Leschziner et al. 2007; Chaban et al. 2008).

RSC remodels nucleosomes throughout the genome, regulating the positions and densities of histones near the promoters of genes transcribed by RNA polymerase II (Pol II), as well as genes transcribed by Pol III (Parnell et al. 2008; Hartley and Madhani 2009), and its activity affects the transcription state of both classes of genes.

Rsc2 is required for insulator boundary function at the *HMR* locus, and its mutation leads to a loss of the nucleosome-depleted region encompassed by the insulator (Dhillon et al. 2009). Additionally, loss of Rsc2 impairs HR and nonhomologous end joining (NHEJ), the two DSB-repair pathways, along with repair of DNA damaged by UV light (Chai et al. 2005; Shim et al. 2005; Srivas et al. 2013). Rsc2 is present at kinetochores and is required for proper sister chromosome cohesion and chromosome segregation (Hsu et al. 2003; Baetz et al. 2004), as well as maintenance of telomeres (Askree et al. 2004).

Brahma-Associated Protein (BAP) AND Polybromo-Associated BAP (PBAP) IN *Drosophila melanogaster*

The BAP Complex

Complexes similar to yeast SWI/SNF were discovered in *Drosophila* based on their ability to oppose *Polycomb* repressive activity (Kennison and Tamkun 1988; Tamkun et al. 1992). The central ATPase of this complex is the gene product of *brahma* (*brm*), giving rise to the name BAP complex. The BAP complex is defined as containing OSA and lacking BAP170, SAYP, and POLYBROMO (Fig. 1) (Mohrmann et al. 2004; Bouazoune and Brehm 2006; Chalkley et al. 2008).

In flies, the activating Trithorax group genes generally oppose the repressive activity of Polycomb group genes. Misregulation of developmental genes results in aberrant morphologies and ectopic locations of body parts. Proteins encoded by *brahma*, *osa*, and *moira* (*mor*) are

members of the Trithorax group, a set of factors that oppose the repressive activity of Polycomb-group proteins (Kennison and Tamkun 1988; Tamkun et al. 1992; Papoulas et al. 1998; Collins et al. 1999; Crosby et al. 1999; Kal et al. 2000; Simon and Tamkun 2002; Kingston and Tamkun 2014).

Although Polycomb genes are conserved in animals, plants, and some fungi (Shaver et al. 2010), unicellular model yeasts lack Polycomb, suggesting that multicellular organisms have greater needs for repressive factors (as well as their regulators) for lineage-specific functions during development. As discussed below, failure to oppose Polycomb repressive activity in mammals plays an important role in malignancy. Nevertheless, despite this important regulatory role (likely present in the last common eukaryotic ancestor), the precise mechanisms of Polycomb opposition remain murky.

The PBAP Complex

Drosophila have a second BRM-containing complex, named PBAP. The subunit compositions of the BAP and PBAP complexes bear similarities to the functional specialization between SWI/SNF and RSC in yeast. PBAP complexes lack OSA and instead contain BAP170, SAYP, and POLYBROMO (Mohrmann et al. 2004; Bouazoune and Brehm 2006; Chalkley et al. 2008). Interestingly, BAP and PBAP subunits both genetically oppose Polycomb-mediated silencing, without regard to whether they are common to BAP and PBAP, or exclusive to one of the complexes (Kennison and Tamkun 1988; Tamkun et al. 1992; Papoulas et al. 1998; Collins et al. 1999; Crosby et al. 1999; Kal et al. 2000; Simon and Tamkun 2002). On the other hand, the complexes can also have distinct or even opposing functional roles. For example, PBAP but not BAP is required for germinal stem-cell maintenance (He et al. 2014). Moreover, BAP and PBAP have opposing roles in *Egfr* expression in wing development; although BAP positively regulates *Egfr* expression (Molnar et al. 2006; Terriente-Felix and de Celis 2009), PBAP instead negatively regulates *Egfr* (Rendina et al. 2010). Together, these observations suggest that mutations in different subunits or complexes may result in distinct or even opposing changes to the genomic landscape, a fact that complicates straightforward predictions of their effects.

One clue regarding the distinct functions of BAP and PBAP complexes comes from microscopic examination of polytene chromosomes. Polytene chromosomes arise from successive rounds of replication without cell division, resulting in many copies of aligned condensed sister chromatids (Balbiani 1881). Visualization of chromatin domains using immunofluorescence shows that BAP and PBAP complexes have both overlapping and mutually exclusive domains. Polycomb domains are largely not found at both the overlapping and mutually exclusive BAP/PBAP domains (Armstrong et al. 2002; Mohrmann et al. 2004; Moshkin et al. 2007). This pattern suggests that BAP and PBAP work both cooperatively and independently at distinct sites to oppose Polycomb silencing.

BAF AND PBAF IN MAMMALS

BAF Complexes

In mammals, highly polymorphic BAF complexes (Wang et al. 1996a,b) are composed of a single central ATPase, either BRG (SMARCA4) or BRM (SMARCA2), and several BRG-/BRM-associated factors (BAF subunits) (Khavari et al. 1993). In addition to the subunits homologous to those in *Drosophila* or yeast, several other subunits appear to be dedicated to vertebrate or mammalian complexes, including SS18/SS18L1, BCL7A/B/C, BCL11/A/B, and BRD9 (see Fig. 1). Scanning force microscopy of BAF complexes isolated from HeLa cells show objects with similar appearances and dimensions as yeast SWI/SNF or RSC (Schnitzler et al. 2001); however, BAF subunits are frequently inactivated in long-term cell lines, and so caution is warranted when inferring the complex's characteristics based on immortalized cancer lines.

ChIP-seq studies in many cell types show that BAF complexes bind 20,000–40,000 sites genome-wide, with broad binding sites sometimes spanning 2–5 kbp, suggesting that more

than one complex may operate at a given site (Ho et al. 2009a; Euskirchen et al. 2011). BAF complexes have many roles in development (Ho and Crabtree 2010); the presence of BAF complexes on chromatin correlates with enhancers (Rada-Iglesias et al. 2011), and its activity regulates a variety of important biological processes ranging from self-renewal and pluripotency in embryonic stem cells (Ho et al. 2009b), to cardiac development (Lickert et al. 2004), and neural differentiation (Yoo et al. 2009). BAF activity and transcription factor (TF) binding appear to be coupled idiosyncratically, as examples can be found in which TF binding requires BAF activity (Ho et al. 2011; Bao et al. 2015) or, alternatively, in which recruitment of BAF requires existing TF binding (Liu et al. 2001). Some of the complexes' subunits are tissue-specific; for example, BAF53B (ACTL6B), BAF45B (DPF1), and SS18L1 (CREST, a Ca^{2+}-responsive regulator), are found only in BAF complexes of mature, postmitotic neurons (Olave et al. 2002; Aizawa et al. 2004; Lessard et al. 2007; Staahl et al. 2013). BAF subunit composition is subject to tight regulation, as miRNA-based repression of *BAF53A* occurs either before or coincident with the last mitotic division of neurons (Yoo et al. 2009), and failure to express neural-specific subunits like BAF53B leads to defects in synaptogenesis and dendritic outgrowth (Lessard et al. 2007; Vogel-Ciernia et al. 2013). BAF subunit composition also contributes substantially to cell reprogramming (Singhal et al. 2010; Yoo et al. 2011), an instructive effect seemingly incompatible with simple mechanisms of nucleosome mobilization.

Before the modern tumor-sequencing era, the frequent absence of core BAF subunits in immortalized cell lines prompted early speculation that BAF subunits were tumor suppressors (Dunaief et al. 1994). Screening for *BRG* mutations revealed widespread defects in a number of different cancer cell lines, and ectopic expression of *BRG* in these lines often results in altered morphology (Wong et al. 2000). Moreover, many cell lines down-regulate both BRG and BRM ATPases (Reisman et al. 2002). In cultured cells, BAF complexes missing the core ATPase fail to bind the tumor suppressor RB1 and suppress E2F1 (Dunaief et al. 1994; Trouche et al. 1997), although it remains uncertain whether this feature reflects its central role in primary tumors. Moreover, as described below, several specific malignancies are driven entirely by BAF subunit dysfunction. Abundant evidence now shows that BAF complexes act as major tumor suppressors.

PBAF Complexes

PBAF complexes were first discovered by Tjian and colleagues in a search for factors that activated ligand-mediated transcription on nucleosomal templates (Lemon et al. 2001). PBAF complexes contain PBRM1 and ARID2 but lack ARID1A/B. PBAF complexes also contain BRD7 in place of BRD9 (Kaeser et al. 2008), BAF45A (PHF10) instead of BAF45B/C/D (DPF1/3/2), and lack SS18 (see Fig. 1) (Middeljans et al. 2012). EM reconstruction of PBAF complexes from HeLa cells show heterogeneous >1-MDa structures with similarities to RSC from yeast (Leschziner et al. 2005); however, because BAF and PBAF complexes are combinatorially assembled, the origin of the observed heterogeneity of these structures remains uncertain. Several subunits share some homology with subunits of the yeast RSC complex, and like RSC, PBAF complexes show significant occupancy at the kinetochores of mitotic chromosomes (Xue et al. 2000), suggesting an important conserved role in cell division.

PBAF subunits regulate cell differentiation and may be an important regulator of cell-type identity (Bajpai et al. 2010; Xu et al. 2012). Additionally, a large body of evidence shows that PBAF complexes have important roles in the maintenance of genomic integrity during mitosis, described in more detail below (see section on Nontranscriptional Roles of BAF/PBAF Complexes in Cancer).

BAF AND PBAF SUBUNITS ARE FREQUENTLY DISRUPTED IN CANCER

In mammals, 28 genes have been discovered to date with close sequence homology with the yeast Snf2 ATPase (Fig. 2A). Despite sharing

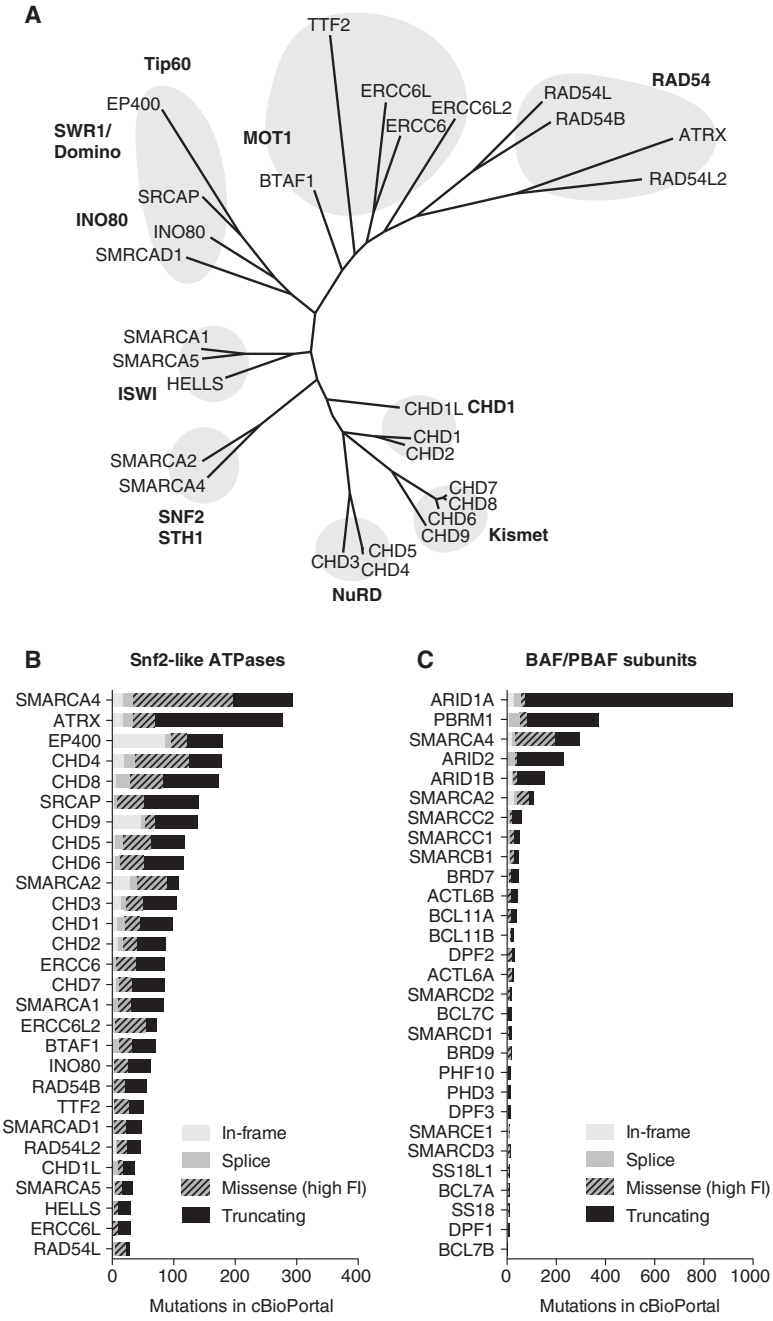


Figure 2. The family of human Snf2-like ATPases and their differing roles in cancer. (*A*) Human Snf2-like ATPases cluster into groups based on degree of sequence similarity. The chromatin remodelers from model organisms are shown near these groups in bold. Radial dendrogram constructed using TreeDyn (Chevenet et al. 2006). (*B*) Human Snf2-like ATPases are mutated at different frequencies across all cancer types. The total number of mutations appearing in cBioPortal (including public datasets from The Cancer Genome Atlas (TCGA), Cancer Cell Line Encyclopedia (CCLE), and others cited in the text) is summed for each gene and presented by the type of mutation. Missense mutations predicted to have neutral, low, or medium functional impact are not shown because of the unknown nature of their effects and increased likelihood to be background mutations. (*C*) The number of mutations of each BAF/PBAF subunit is presented as in *B*. *ARID1A* and *PBRM1* frequently undergo truncating mutation, but *BRG* (*SMARCA4*) frequently has missense mutations with high functional impact.

highly conserved Snf2-like ATPase domains, these ATPases play distinct biological roles and are nearly all functionally nonredundant between the different remodeling families, as reviewed elsewhere (Clapier and Cairns 2009). Based on their distinct biological activities, disruption of each of these remodelers is under a different selection pressure in cancer, resulting in a wide range of mutation frequencies (Fig. 2B). Across all cancer types, ~20% of human malignancies have defects in BAF-related complexes (Kadoch et al. 2013; Shain and Pollack 2013) making them among the most frequently mutated chromatin regulatory complexes in malignancy.

In addition to their ATPases BRG and BRM (Khavari et al. 1993), BAF and PBAF complexes contain a number of noncatalytic subunits that contribute to targeting of the complex to cognate loci, or have other unknown functions. BAF and PBAF complexes collectively contain eight bromodomains (six on PBRM1, one on either BRG or BRM, and one on BRD7 or BRD9), a region homologous with chromodomains (BAF155/170), two PHD finger proteins (BAF45 subunits), a large number of zinc finger and other DNA-binding domains that bind distinct architectural features such as AT-rich sequences or HMG recognition features (Wang et al. 1996a,b, 1998; Lessard et al. 2007). Some of these subunits are among the most frequently mutated genes in cancer, and highly subunit-specific mutation patterns contribute to different cancer types (Figs. 2C and 3). Below, we summarize the role of these subunits in the complex, and discuss their contribution to malignancy.

BRG (*SMARCA4*) Is Mutated in Many Different Malignancies

As defined by the overall number of truncating and high-functional-impact mutations, *BRG* is the most frequently mutated Snf2-like chromatin remodeling ATPase in cancer (Fig. 2C). Unlike many other tumor suppressors, hypermethylation and silencing of *BRG* is reported to be relatively uncommon (Medina et al. 2004; Ramos et al. 2014). However, heterozygous and biallelic inactivation of *BRG* occurs in tumors of the breast (The Cancer Genome Atlas 2012b), lung (The Cancer Genome Atlas 2014c), stomach (The Cancer Genome Atlas 2014a), bladder (The Cancer Genome Atlas 2014b), colon (The Cancer Genome Atlas 2012a), and in several other tumor types and cell lines (Wong et al. 2000). Disruption of *BRG* is especially common in small cell ovarian cancer (90%–100%) (Jelinic et al. 2014; Ramos et al. 2014), cancers of the skin (up to 27%) (Hodis et al. 2012; Li et al. 2015; Shain et al. 2015; The Cancer Genome Atlas 2015), diffuse large B-cell lymphoma (10%), and non-small-cell lung cancers (~11%) (Imielinski et al. 2012; Rizvi et al. 2015), in which it has been reported as the fifth most frequently mutated gene (Medina et al. 2004). In some specific malignancies, such as certain thoracic sarcomas (Le Loarer et al. 2015), biallelic inactivation of *BRG* occurs at elevated frequencies. Although it was initially thought that in most cancers *BRG* mutations were generally homozygous (Medina and Sanchez-Cespedes 2008; Medina et al. 2008), it has since been determined that, in many cancer types, a large number of mutations of *BRG* are heterozygous, with many mutations clustering at conserved motifs of the ATPase domain. Accordingly, CRISPR-Cas9 tiling experiments have shown that the ATPase domain contains the most functionally important domain of BRG (Shi et al. 2015).

The ATPase domain of Snf2-like remodelers is composed of two conserved subdomains. The amino-terminal ATPase subdomain of BRG contains several residues highly conserved within the SF2 helicase superfamily (Jankowsky and Fairman 2007; Fairman-Williams et al. 2010). Based on crystal structures of homologous Snf2-like proteins (Durr et al. 2005; Thoma et al. 2005; Wollmann et al. 2011), many of these residues are predicted to contact ATP (Walker et al. 1982) or communicate the strain of ATP binding and hydrolysis to the site of DNA binding to exert mechanical force (Banroques et al. 2008), and are frequently mutated in a number of malignancies (Figs. 3 and 4). Some effects of these mutations have been characterized. For example, K785R and T910M, respectively,

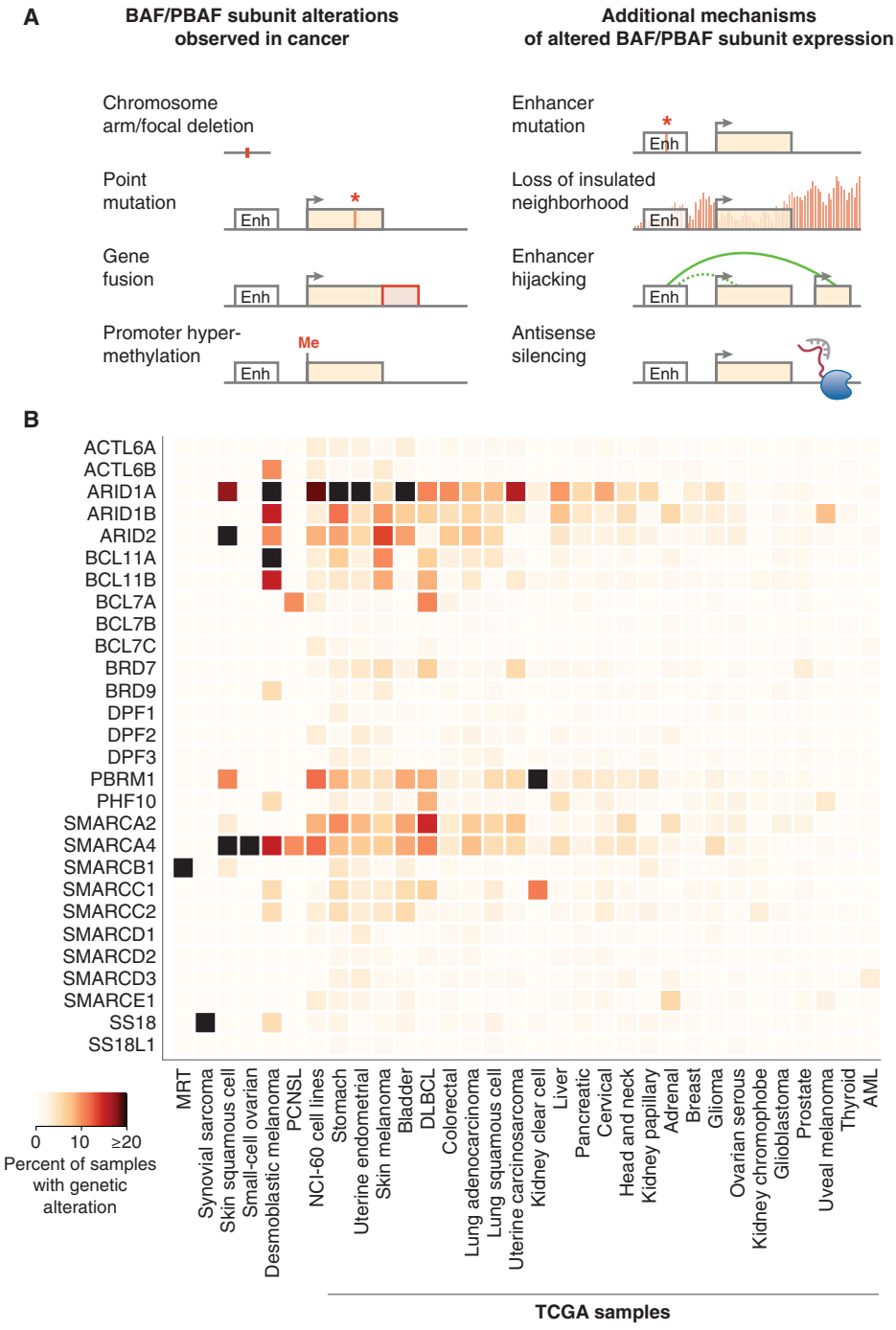


Figure 3. Mutations of BAF and PBAF subunits occur in subunit-specific patterns in cancer. (*A*) (*Left* panel) Illustration of the different types of genetic and epigenetic disruptions that affect BAF/PBAF subunits in cancer. Deletion of chromosome arms or foci leads to loss of a subunit allele, point mutations alter coding sequence, gene fusions lead to altered function, and hypermethylation of promoters associated with loss of expression. (*Legend continues on following page.*)

observed in melanoma (Hodis et al. 2012; The Cancer Genome Atlas 2015), medulloblastoma (Pugh et al. 2012), and several cancer cell lines, have severely reduced ATPase activity, leading to anaphase bridges and failure of topoisomerase IIa to bind DNA (Dykhuizen et al. 2013) (discussed in greater detail below). Adjacent residues are mutated in a number of different cancer types, suggesting that functional inactivation contributes to diverse malignancies. In other ATP-dependent remodelers, dominant-negative mutations result in phenotypes distinct from subunit deletion (Corona et al. 2004; Skene et al. 2014), suggesting that the particular mechanisms of inactivation may lead to different downstream effects.

Although the details remain murky, the carboxy-terminal subdomain of Snf2-like ATPases appears to cooperate with the amino-terminal subdomain to exert large-scale motions needed to translocate along DNA (Durr et al. 2005) but may also carry out some other uncharacterized activity. In the carboxy-terminal ATPase subdomain of BRG, R1192 is recurrently mutated in cancer of the stomach, liver, lung, melanoma, esophagus, and breast, as well as in gliomas (Figs. 3 and 4). Moreover, the homologous position is also mutated in *BTAF1*, *CHD1*, and *ATRX* in several different malignancies, suggesting this well-conserved position may be an Achilles' heel of Snf2-like remodelers. Other nearby mutations at conserved residues in Motif V of the carboxy-terminal subdomain severely compromise ATPase activity in the yeast SWI/SNF complex (Richmond and Peterson 1996; Smith and Peterson 2005). Although it is clear that commonly observed point mutations disrupt or completely abolish ATPase activity, a complete accounting of the downstream effects of these mutations in malignancy has not yet been performed.

BRM, the paralog of BRG that is not a subunit of the PBAF complex, also shows similar clustering of mutations at the amino- and carboxy-terminal helicase-like subdomains, but is much less frequently mutated in cancers (Figs. 3 and 4). Interestingly, several in-frame deletions in the QLQ domain of BRM have been observed in primary tumors and several cancer cell lines (Reinhold et al. 2012). BRM and homologs are regulators of splicing (Batsche et al. 2006; Tyagi et al. 2009; Waldholm et al. 2011; Patrick et al. 2015); however, the effects of its mutation on alternative splicing remain unknown.

ARID1A in Uterine, Colorectal, Stomach, Bladder, and Other Cancers

By far the most frequently disrupted BAF subunit is *ARID1A* (*BAF250A*; Fig. 2B). Large regions of both ARID1A and its paralog ARID1B are low-complexity sequences with unknown function. ARID1A and ARID1B both contain an ARID DNA-binding domain as well as a homologous domain of unknown function (currently designated DUF3518 in Pfam; Fig. 4). Although the function of this carboxy-terminal domain has not yet been described, it has been speculated to have ubiquitin ligase activity (Li et al. 2010).

Among the earliest reports of the complex's tumor-suppressor role was the discovery that ~50% of ovarian clear cell carcinomas and endometriosis-associated ovarian carcinomas contain inactivating *ARID1A* mutations (Jones et al. 2010; Wiegand et al. 2010). Mutations of *ARID1A* have since been observed at high frequency in a number of studies, including uterine

Figure 3. (*Continued*) (*Right* panel) Mechanisms leading to altered BAF/PBAF subunit expression in cancer may also include mutations in enhancers, loss of insulated neighborhoods leading to spreading of heterochromatin over BAF/PBAF genes, enhancer hijacking, and antisense silencing. (*B*) Heat map of the frequency of subunit alterations across cancer types (frequency includes all nonsilent mutations, biallelic deletions, and gene fusions). Mutation frequencies for malignant rhabdoid tumor (MRT) and synovial sarcoma are inferred from available cytogenetic and mutation data, as described by works cited in the main text. All other data obtained from studies cited in the main text. PCNSL, Primary central nervous system lymphoma; DLBCL, diffuse large B-cell lymphoma; AML, acute myeloid leukemia.

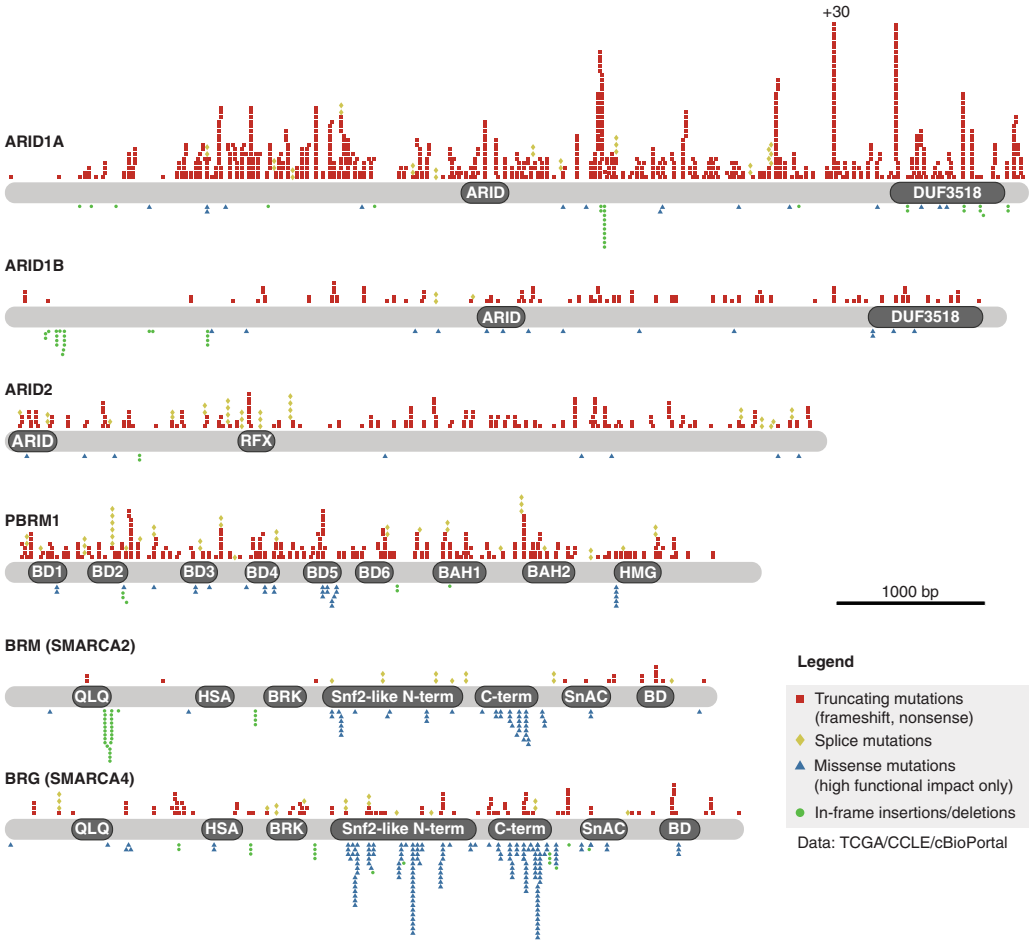


Figure 4. Cancer mutations of BAF/PBAF subunits arise in characteristic patterns. *ARID1A*, *ARID2*, and *PBRM1* are primarily affected by truncating mutations. The ATPases *BRG* and *BRM* show a high tendency for missense mutations at the conserved Snf2-like ATPase domains. Missense mutations predicted to have neutral, low, or medium functional impact are not shown because of the unknown nature of their effects and increased likelihood to be background mutations. N-term, Amino terminal; C-term, carboxy terminal.

endometrial carcinoma (34%) (Kandoth et al. 2013), colorectal cancers (10%) (The Cancer Genome Atlas 2012a), as well as cancers of the bladder (29%) (Gui et al. 2011), stomach (34%) (Wang et al. 2011a, 2014), cholangiocarcinomas (27%) (Jiao et al. 2013), neuroblastomas (11%) (Sausen et al. 2013), and pancreas (~5%) (Biankin et al. 2012). These recurrent loss-of-function mutations make ARID1A the premier tumor-suppressor subunit of the BAF complex; however, very little is known about the mechanisms of how this subunit contributes to malignancy.

Mutations of *ARID1A* are most frequently truncating mutations (frameshifts and nonsense mutations (Figs. 2C and 4), which may be degraded by nonsense-mediated decay. Although the ARID domain in mice is critical for the function of the protein, mutations in human cancer are not especially localized to the ARID domain; indeed no missense mutations expected to be of high functional impact have currently been reported in the ARID domain (Fig. 4). The few missense mutations present are generally predicted to have low or

medium functional impact and are distributed uniformly over the gene. The hotspots of truncating mutations that occur are explained in part by frequent *ARID1A* mutations arising in tumors with mutated DNA polymerase ε (*POLE*). As a result of failed leading-strand proofreading during replication, *POLE*-mutated tumors often have huge numbers of C>T transitions, many of which convert arginine codons (CGA) to stop codons (TGA) (Alexandrov et al. 2013). Biallelic inactivation of *ARID1A* does occur, but in many cases (particularly in gastric and endometrial cancer) mutations occur in only a single allele (Kandoth et al. 2013). However, hypermethylation of the *ARID1A* promoter has been observed in many breast cancers; hence, epigenetic silencing mechanisms are also common (Zhang et al. 2013).

In ovarian cancer, mutation of *ARID1A* frequently co-occurs with activating mutations of phosphatidylinositol 3-kinase (*PI3K*). Interestingly, BRG binds the PI3K substrate PIP_2 (phosphatidylinositol 4,5-bisphosphate), a phospholipid with several roles in signaling and a regulator of actin-related proteins. Binding of PIP_2 by *Brg* regulates association of the complex with actin (Rando et al. 2002); therefore, activating mutations of PI3K may deplete PIP_2, leading to altered BAF localization or function (Zhao et al. 1998). Mice with *ARID1A*/*PI3K* double mutations, but not mice with only a single *ARID1A* or *PI3K* mutation, develop ovarian tumors with features similar to ovarian clear cell carcinoma (Chandler et al. 2015), suggesting the effects of PIP_2 may be mediated through ARID1A-containing complexes and providing new insight into the cooperation of these two genes in cancer.

ARID1B is mutated in several malignancies and, like *ARID1A*, these mutations are also mostly truncating (Fig. 4). However, *ARID1B* mutations are not as frequent as those of *ARID1A* (Fig. 2C). This discrepancy may reflect important functional differences between these two genes, or may instead reflect *ARID1B* expression in fewer cell types. Interestingly, *ARID1B* has been identified as one of the most important genes involved in neurodevelopmental disorders (Santen et al. 2012; Tsurusaki et al. 2012; Deciphering Developmental Disorders Study 2015), further illustrating the relevance of combinatorial subunit assembly of BAF complexes to development and human diseases.

PBRM1 in Clear Cell Renal Carcinoma

PBRM1 (BAF180, Polybromo) is named for the presence of six bromodomains in the protein, and is a defining subunit of the PBAF complex. In renal clear cell carcinoma (ccRCC), mutation or loss of *PBRM1* occurs in ~41% of cases (Varela et al. 2011), making it the second-most frequently mutated gene in ccRCC. Like *ARID1A* in other cancers, the majority of mutations of *PBRM1* in ccRCC are truncating mutations (Figs. 2C and 4), which may not result in protein expression because of nonsense-mediated decay. However, many ccRCC cases have biallelic inactivation of *PBRM1*, through loss of one allele via focal/chromosomal deletion at chromosome arm 3p, and an inactivating mutation on the remaining allele. Furthermore, hypermethylation of the *PBRM1* promoter is generally absent in ccRCC (Ibragimova et al. 2013), indicating that inactivation occurs primarily through mutation or deletion. Some tumors do contain missense mutations, and although their functional impacts remain uncertain, their presence suggests a degree of nonredundancy between these domains. Although most bromodomains bind acetylated lysines from histones, the role of PBRM1's bromodomains toward targeting of PBAF complexes remains uncertain.

In ccRCC, *PBRM1* inactivation frequently coincides with mutation of the *VHL* (von Hippel–Lindau) tumor suppressor. Because of their close proximity on chromosome arm 3p, focal and chromosome arm-level deletions frequently affect both of these genes simultaneously. However, the striking frequency of inactivating point mutations of *PBRM1* alongside *VHL* and *BAP1* mutations suggests that joint inactivation of these genes may potentiate the oncogenic nature of these defects (Gerlinger et al. 2014).

Like *PBRM1*, *ARID2* (*BAF200*) encodes another subunit dedicated to PBAF complexes. *ARID2* is not a homolog of *ARID1A*/*B*, but is

instead mutually exclusive with *ARID1A/B*, although the shared presence of an AT-rich interaction domain (ARID) in these three subunits suggests some common structural similarities. *ARID2* is frequently mutated in other malignancies but is apparently not targeted in ccRCC as frequently as *PBRM1*, suggesting that PBRM1 has an important and distinct functional role as a member of the PBAF complex in kidney cells. ARID2 has been reported to contribute to repression (Raab et al. 2015), and is frequently mutated in melanoma (Hodis et al. 2012; Ding et al. 2014; Lee et al. 2015), non-small-cell lung cancer (Manceau et al. 2013), as well as in ~18% of hepatitis-associated hepatocellular carcinomas (Li et al. 2011). Moreover, the discovery of frequent joint inactivation of *PBRM1*, *ARID2*, and *BAP1* in biliary-phenotype-displaying subtype of hepatic carcinomas (Fujimoto et al. 2015) suggests that in some contexts they may contribute to malignancy in a cooperative manner.

SMARCB1 in Malignant Rhabdoid Tumors

Perhaps the best-characterized example of a tumor-suppressor role for ATP-dependent chromatin remodeling comes from malignant rhabdoid tumors (MRTs). MRTs are rare but highly lethal childhood cancers that are caused by biallelic inactivation of *SMARCB1* (*BAF47*, *SNF5*, or *INI1*), which occurs in nearly all cases (Versteege et al. 1998; Roberts et al. 2000). The classic loss of heterozygosity observed for *SMARCB1* leads to aberrant activation of Hedgehog-Gli and Wnt/β-catenin pathways (Jagani et al. 2010; Mora-Blanco et al. 2014), and importantly, impairs the ability of BAF/PBAF complexes to regulate the placement and function of Polycomb repressive complexes. As a result of failure to oppose Polycomb, the repressive mark H3K27me3 accumulates at the tumor suppressor *p16/INK4A* (*CDKN2A*) locus (Wilson et al. 2010). The impaired opposition to Polycomb repression plays an important role in cancer, reminiscent of BAP/PBAP complexes throughout development in flies (Tamkun et al. 1992).

MRTs have remarkably stable diploid genomes except for deletions and mutations at chromosome *22q*, where *SMARCB1* is located (McKenna et al. 2008; McKenna and Roberts 2009; Lee et al. 2012). Exome sequencing also shows that these tumors have among the lowest mutational loads of any human tumor sequenced to date (Lawrence et al. 2014). Finally, ectopic expression of *SMARCB1* reverses Polycomb silencing at the tumor suppressor *p16/INK4A* locus, leading to cellular senescence (Oruetxebarria et al. 2004; Kia et al. 2008), indicating that these tumors are driven exclusively by epigenetic regulation (except for the original genetic inactivation of *SMARCB1*). In addition to MRTs, *SMARCB1* appears to play a role in a number of cancers and other neoplastic disorders, including prostate cancer, epithelioid sarcomas, familial schwannomatosis, and renal medullary carcinomas (Roberts and Biegel 2009; Prensner et al. 2013). Biallelic inactivation of *SMARCB1* has also been reported in 7%–10% of Ewing sarcomas (Jahromi et al. 2012).

In mouse models, conditional deletion of *SMARCB1* leads to T-cell lymphomas with short latency and 100% penetrance (Wang et al. 2011b), suggesting that *SMARCB1* inactivation can cause fast transformation alone without other genetic changes, as observed in MRTs. Interestingly, rhabdoid tumors are not seen in mice with *SMARCB1* inactivation, attesting to the tissue-specific and species-specific function of the complexes. Importantly, the pathogenesis of most human malignancies with BAF/PBAF mutations may be different from that of MRTs. With the exception of some noteworthy examples described below, the majority of cancers bearing BAF/PBAF subunit mutations are found in older age groups, in which tumors have long latencies, are highly mutated, and are genomically unstable. Thus, the low mutation rates observed in MRTs may be because of the extremely short latency between biallelic inactivation and transformation, which may not allow accumulation of mutations resulting from impairment of the complex's other functions.

SS18 in Synovial Sarcoma

Synovial sarcoma is an aggressive, poorly differentiated, stem-cell-like soft-tissue malignancy that typically arises in the extremities of young

adults. The hallmark of synovial sarcoma is a highly characteristic translocation of chromosomes 18 and X, which fuses the dedicated BAF subunit SS18 (Middeljans et al. 2012) to the SSX fusion partner on the X chromosome (Crew et al. 1995; Naka et al. 2010). This fusion occurs in nearly all cases and in some cases is the only known cytogenetic abnormality. Despite the continued existence of the remaining wild-type SS18 allele and unaltered BAF47 alleles, the SS18–SSX fusion is preferentially assembled into the BAF complex concomitant with complete loss of BAF47 from the complex. BAF complexes containing the SS18–SSX fusion are retargeted to oncogenic loci such as *SOX2* and *PAX6*, where removal of the repressive histone mark H3K27me3 results in transformation (Kadoch and Crabtree 2013).

Forced overexpression of wild-type SS18, or shRNA-mediated knockdown of the SS18–SSX fusion, is sufficient to reverse oncogenic BAF subunit composition. Reversion leads to increased levels of H3K27me3 at *SOX2* and other oncogenic loci, and loss of proliferation (Kadoch and Crabtree 2013), indicating that transformation is maintained through epigenetic mechanisms. The reversible and remarkably specific pathogenesis of synovial sarcoma suggests that this tumor may be an attractive candidate for development of therapeutics.

A number of similarities exist between synovial sarcoma and MRTs. They are both childhood malignancies driven by a defining alteration of a single BAF subunit, and senescence can be achieved by repair of the affected subunit. Moreover, SMARCB1 activity is abolished in both cancers, albeit through different mechanisms. However, in contrast to MRTs, which transform by failing to oppose Polycomb activity at *p16/INK4A*, the genetic dominance of the SS18–SSX fusion in synovial sarcoma arises from its preferential assembly into BAF complexes, and its apparent ability to retarget the complex and oppose Polycomb at oncogenic loci (Kadoch and Crabtree 2013).

BAF53A and the Role of Nuclear Actin/ARPs

BAF53A (*ACTL6A*) is an ARP and a subunit of BAF/PBAF complexes that is rarely mutated in cancer. Instead, *BAF53A* frequently undergoes amplification in squamous cell malignancies from many different tissues of origin. BAF53A is required for maintenance of hematopoietic stem cell identity (Krasteva et al. 2012), and also maintains a progenitor state in epidermal cells by repressing *KLF4*, an activator of differentiation (Bao et al. 2013). Recent work has also shown that *BAF53A* is a target of miR-206, a microRNA missing in rhabdomyosarcomas (RMS). The resulting up-regulation of *BAF53A* in RMS cells contributes to the failure of myogenic cells to properly differentiate (Taulli et al. 2014), whereas its silencing inhibits proliferation of RMS cells, suggesting that BAF53A promotes proliferation and interferes with differentiation. Therefore, it is appealing to speculate that BAF53A may generally have oncogenic or mitogenic role in many cell types, perhaps based on interaction with the BRG/BRM helicase-SANT-associated (HSA) domain (Zhao et al. 1998; Rando et al. 2002; Szerlong et al. 2008). Ablation of the HSA domain from Sth1, the ATPase of RSC in yeast, causes the specific loss of ARPs from the complex, and a reduction in the activity of the ATPase.

ARPs are genetically essential subunits of SWI/SNF-like remodelers (Shen et al. 2003; Wu et al. 2007), and the interaction of actin and ARPs with the HSA domain from Snf2-like ATPases has long been thought to regulate their activity. Although complexes reconstituted without actin or ARPs can achieve remodeling activity comparable to intact complexes in vitro (Phelan et al. 1999), BAF53A/B is required for BAF function in vivo. The crystal structure of the Snf2 HSA domain with Arp7 and Arp9 shows that actin filament formation is unlikely because of the incompatible position adopted by the ARPs (Schubert et al. 2013). Thus, rather than binding filamentous actin, the ARPs in the complex may instead modulate ATPase activity or the coupling of ATP hydrolysis to remodeling activity.

Important structural differences exist between the yeast complexes and human complexes (Zhao et al. 1998). In yeast, both the SWI/SNF and RSC complexes contain Arp7 and Arp9 as obligate heterodimers (Szerlong et al.

2003), but lack actin itself (Cairns et al. 1998; Peterson et al. 1998). In contrast, BAF and PBAF complexes contain BAF53A/B and actin (Zhao et al. 1998). Therefore, it remains unclear whether the structures from yeast also apply directly to the mammalian complexes. As a result, it remains unknown how excess BAF53A may affect the activity of BAF and PBAF complexes.

NONTRANSCRIPTIONAL ROLES OF BAF/PBAF COMPLEXES IN CANCER

Involvement in DNA Repair and Chromosome Stability

In addition to their well-established roles as epigenetic regulators described above, BAF/PBAF complexes have several nontranscriptional roles that also contribute to malignancy. One nontranscriptional role in cancer is found in DNA-repair pathways. Various mechanisms have been proposed for recruitment of BAF/PBAF complexes to sites of DNA damage, including ATM-/ATR-dependent phosphorylation of BAF170 (Peng et al. 2009), and a direct interaction between γ-H2A.X and the BRG bromodomain (Lee et al. 2010). In addition, evidence now points to roles for BAF and PBAF in both NHEJ and HR pathways (Ogiwara et al. 2011; Watanabe et al. 2014; Brownlee et al. 2015; Qi et al. 2015). Therefore, in humans, BAF and PBAF complexes may help protect genomic integrity similar to the INO80 complex in budding yeast (Gerhold et al. 2015), which interestingly is not frequently mutated in cancer.

In addition to well-established pathways of DNA repair, PBAF complexes have other important roles for maintaining genomic stability. PBRM1 plays a critical role in sister chromatid cohesion, in which misregulation leads to genome instability, anaphase bridges, and aneuploidy (Brownlee et al. 2014). PBRM1 also plays a role in repriming stalled replication forks similar to yeast RSC complexes (Askree et al. 2004). Stalled replication forks are common sites of DNA damage, providing another important mechanism for ensuring genome integrity (Niimi et al. 2012). Recently, roles for PBAF but not BAF have been identified in DNA-damage-induced transcriptional repression that involves PRC1/2 subunits (Kakarougkas et al. 2014), and ubiquitination of PCNA following DNA damage (Niimi et al. 2015).

BAF and PBAF subunits occupy regions that are critical for chromosome organization, such as the binding sites of CTCF (CCCTC-binding factor), cohesins, lamin, and replication origins (Euskirchen et al. 2011). In addition to the loop anchor sites formed by CTCF and cohesins, which appear to be master regulators of topological domains in stem cells and cancer cell lines (Kagey et al. 2010; Dixon et al. 2012; Yan et al. 2013; Dowen et al. 2014; Ji et al. 2015), several other chromatin organizational elements have been identified in eukaryotes, such as tRNA genes (Kirkland et al. 2013), repetitive elements (Lunyak et al. 2007), transposons (Lippman et al. 2004), and PRC1-binding sites (Bantignies et al. 2011; Schoenfelder et al. 2015; Wani et al. 2016). Chromatin architectural sites are often subject to epigenetic regulation (Bell and Felsenfeld 2000; Wang et al. 2012) and show significant BAF and PBAF enrichment (Euskirchen et al. 2011), suggesting that BAF and PBAF may play important roles in regulating overall chromatin architecture.

Synergy between BAF and Topoisomerase Function

Topoisomerases require nucleosome-free DNA (Sperling et al. 2011), and mutants of BRG that impair ATPase activity induce loss of topoisomerase IIa (TOP2A) binding to DNA, leading to topological defects, anaphase bridges, and partial arrest at the relatively uncharacterized decatenation checkpoint (Dykhuizen et al. 2013). Lung cancer cell lines with *BRG* mutations show increased sensitivity to topoisomerase II inhibitors when EZH2 is also inhibited (Fillmore et al. 2015), suggesting interplay between BAF, TOP2A, and PRC2 in the maintenance of chromatin topology. The importance of BAF's activity toward TOP2A function was recently underlined by the observation that mutations in BAF subunits predict responses to treatment with TOP2A inhibitors (Pang et al. 2015; Wijdeven

et al. 2015). Importantly, the mechanism of opposition to EZH2 consists of more than opposing its methyltransferase activity (Kim et al. 2015), and may underlie an aspect of BAF's tumor-suppressor function with significant clinical importance.

TARGETING TUMORS WITH BAF/PBAF DEFICIENCIES

Recent reports suggest new approaches for targeting tumors with altered BAF/PBAF complexes based on synthetic lethality. In several tumor types, inactivation of one BAF/PBAF subunit induces dependency on the continued expression of that subunit's paralog. For example, tumors with *BRG* mutations frequently depend on the expression of *BRM* (Aguirre et al. 2014; Wilson et al. 2014), whereas tumors with *ARID1A* mutations often depend on *ARID1B* (Helming et al. 2014). Targeting these genetic dependencies represents a novel strategy to attack these tumors. Additionally, loss-of-function of BAF/PBAF subunits may lead to increased Polycomb activity; therefore, inhibition of Polycomb silencing may be beneficial for patients with tumors bearing BAF/PBAF deficiencies. However, the effectiveness of these approaches may depend greatly on the downstream consequences of BAF/PBAF dysfunction within each cell type. For example, PRC2 inhibition may be more beneficial for MRTs than for synovial sarcoma, based on the molecular mechanisms of transformation described above, illustrating the continuing need to examine the epigenetic mechanisms within each tumor type.

PERSPECTIVE AND CLOSING REMARKS

Although abundant evidence indicates that BAF and PBAF defects contribute to malignancy by altering the epigenetic landscape to regulate transcription, many lines of evidence indicate that these defects have pleiotropic effects, because complexes participate in a number of other important chromatin regulatory processes. In addition to their roles in regulating transcrip-

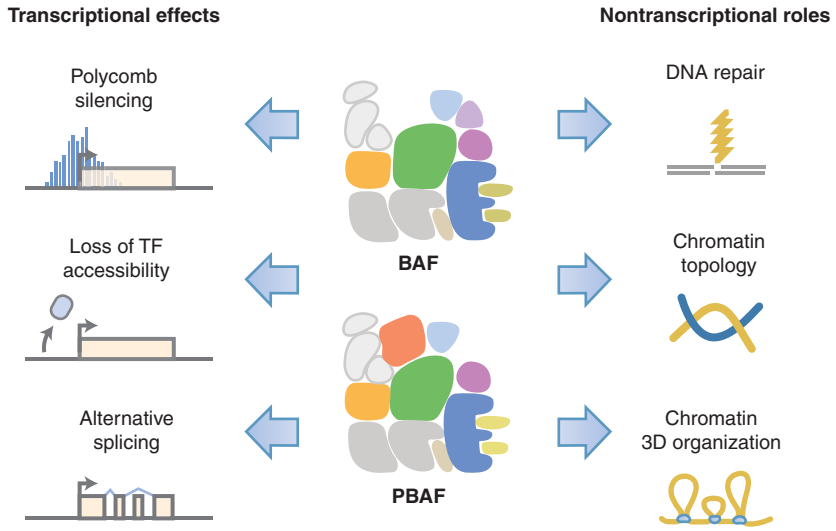


Figure 5. The effects of BAF and PBAF dysfunction in cancer. Dysfunctional BAF/PBAF complexes have been shown to deregulate Polycomb silencing of key tumor suppressors and oncogenes. In model systems, disruption of BAF- and PBAF-like complexes also affects DNA accessibility for transcription and other regulatory factors, and impacts splicing patterns. Given the conserved regulatory roles for BAF- and PBAF-like remodelers in DNA repair, maintenance of chromatin topology and 3D architecture, we anticipate that whole-genome sequencing and new techniques to examine 3D-chromatin architecture may reveal new roles for the complex in addition to its well-defined role as a transcriptional regulator.

tion, a body of work from cancer cell lines and model organisms indicates that BAF- and PBAF-like complexes contribute to several other processes, ranging from DNA recombination and repair to maintenance of 3D chromatin architecture and topology (Fig. 5).

Their numerous roles underscore the fact that the epigenetic state is more than simply a regulatory framework for transcription, but instead represents the sum physicochemical state of the genetic material, which impacts a large number of processes. As a result, the fundamental role of any given BAF and PBAF alteration in cancer is likely to be unique to each cancer type, and may reflect the idiosyncratic processes that drive each malignancy (whether oncogene addiction, autocrine signaling, mutagen exposure, chromosomal instability, etc.). Whole-genome sequencing and various new techniques to examine 3D-chromatin architecture may offer substantial insight into the full breadth of the effects of BAF and PBAF dysfunction, and reveal their diverse contributions toward oncogenesis and tumor biology.

ACKNOWLEDGMENTS

Figures and results reviewed here are based in part on data generated by the The Cancer Genome Atlas Research Network and hosted on cBioPortal (Cerami et al. 2012; Gao et al. 2013). This work is supported by a National Cancer Institute (NCI) career transition award K99CA187565 (C.H.), NCI Grant T32CA009151 (J.G.K.), National Institutes of Health (NIH) Grants R37NS046789 and R01CA163915 (G.R.C.), and the Howard Hughes Medical Institute (G.R.C.).

REFERENCES

Aguirre AJ, Jagani Z, Wang Z, Garraway LA, Hahn WC, Roberts CW, Hoffman GR, Rahal R, Buxton F, Xiang K, et al. 2014. Functional epigenetics approach identifies BRM/SMARCA2 as a critical synthetic lethal target in BRG1-deficient cancers. *Nat Med* **111:** 3128–3133.

Aizawa H, Hu SC, Bobb K, Balakrishnan K, Ince G, Gurevich I, Cowan M, Ghosh A. 2004. Dendrite development regulated by CREST, a calcium-regulated transcriptional activator. *Science* **303:** 197–202.

Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Borresen-Dale AL, et al. 2013. Signatures of mutational processes in human cancer. *Nature* **500:** 415–421.

Armstrong JA, Papoulas O, Daubresse G, Sperling AS, Lis JT, Scott MP, Tamkun JW. 2002. The *Drosophila* BRM complex facilitates global transcription by RNA polymerase II. *EMBO J* **21:** 5245–5254.

Askree SH, Yehuda T, Smolikov S, Gurevich R, Hawk J, Coker C, Krauskopf A, Kupiec M, McEachern MJ. 2004. A genome-wide screen for *Saccharomyces cerevisiae* deletion mutants that affect telomere length. *Proc Natl Acad Sci* **101:** 8658–8663.

Asturias FJ, Chung WH, Kornberg RD, Lorch Y. 2002. Structural analysis of the RSC chromatin-remodeling complex. *Proc Natl Acad Sci* **99:** 13477–13480.

Baetz KK, Krogan NJ, Emili A, Greenblatt J, Hieter P. 2004. The *ctf13-30/CTF13* genomic haploinsufficiency modifier screen identifies the yeast chromatin remodeling complex RSC, which is required for the establishment of sister chromatid cohesion. *Mol Cell Biol* **24:** 1232–1244.

Bajpai R, Chen DA, Rada-Iglesias A, Zhang J, Xiong Y, Helms J, Chang CP, Zhao Y, Swigut T, Wysocka J. 2010. CHD7 cooperates with PBAF to control multipotent neural crest formation. *Nature* **463:** 958–962.

Balbiani E. 1881. Sur la structure du noyau des cellules salivaires chez les larves de *Chironomus* [On the structure of salivary cell nuclei in *Chironomus* larvae]. *Zool Anz* **4:** 662–667.

Banroques J, Cordin O, Doere M, Linder P, Tanner NK. 2008. A conserved phenylalanine of motif IV in superfamily 2 helicases is required for cooperative, ATP-dependent binding of RNA substrates in DEAD-box proteins. *Mol Cell Biol* **28:** 3359–3371.

Bantignies F, Roure V, Comet I, Leblanc B, Schuettengruber B, Bonnet J, Tixier V, Mas A, Cavalli G. 2011. Polycomb-dependent regulatory contacts between distant Hox loci in *Drosophila*. *Cell* **144:** 214–226.

Bao X, Tang J, Lopez-Pajares V, Tao S, Qu K, Crabtree GR, Khavari PA. 2013. ACTL6a enforces the epidermal progenitor state by suppressing SWI/SNF-dependent induction of KLF4. *Cell Stem Cell* **12:** 193–203.

Bao X, Rubin AJ, Qu K, Zhang J, Giresi PG, Chang HY, Khavari PA. 2015. A novel ATAC-seq approach reveals lineage-specific reinforcement of the open chromatin landscape via cooperation between BAF and p63. *Genome Biol* **16:** 284.

Batsche E, Yaniv M, Muchardt C. 2006. The human SWI/SNF subunit Brm is a regulator of alternative splicing. *Nat Struct Mol Biol* **13:** 22–29.

Becker PB, Horz W. 2002. ATP-dependent nucleosome remodeling. *Annu Rev Biochem* **71:** 247–273.

Bell AC, Felsenfeld G. 2000. Methylation of a CTCF-dependent boundary controls imprinted expression of the *Igf2* gene. *Nature* **405:** 482–485.

Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, Miller DK, Wilson PJ, Patch AM, Wu J, et al. 2012. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* **491:** 399–405.

Birrell GW, Giaever G, Chu AM, Davis RW, Brown JM. 2001. A genome-wide screen in *Saccharomyces cerevisiae* for genes affecting UV radiation sensitivity. *Proc Natl Acad Sci* **98:** 12608–12613.

Bouazoune K, Brehm A. 2006. ATP-dependent chromatin remodeling complexes in *Drosophila*. *Chromosome Res* **14:** 433–449.

Brownlee PM, Chambers AL, Cloney R, Bianchi A, Downs JA. 2014. BAF180 promotes cohesion and prevents genome instability and aneuploidy. *Cell Rep* **6:** 973–981.

Brownlee PM, Meisenberg C, Downs JA. 2015. The SWI/SNF chromatin remodelling complex: Its role in maintaining genome stability and preventing tumourigenesis. *DNA Repair (Amst)* **32:** 127–133.

Cairns BR, Kim YJ, Sayre MH, Laurent BC, Kornberg RD. 1994. A multisubunit complex containing the *SWI1/ADR6*, *SWI2/SNF2*, *SWI3*, *SNF5*, and *SNF6* gene products isolated from yeast. *Proc Natl Acad Sci* **91:** 1950–1954.

Cairns BR, Lorch Y, Li Y, Zhang M, Lacomis L, Erdjument-Bromage H, Tempst P, Du J, Laurent B, Kornberg RD. 1996. RSC, an essential, abundant chromatin-remodeling complex. *Cell* **87:** 1249–1260.

Cairns BR, Erdjument-Bromage H, Tempst P, Winston F, Kornberg RD. 1998. Two actin-related proteins are shared functional components of the chromatin-remodeling complexes RSC and SWI/SNF. *Mol Cell* **2:** 639–651.

Cairns BR, Schlichter A, Erdjument-Bromage H, Tempst P, Kornberg RD, Winston F. 1999. Two functionally distinct forms of the RSC nucleosome-remodeling complex, containing essential AT hook, BAH, and bromodomains. *Mol Cell* **4:** 715–723.

Carlson M, Osmond BC, Botstein D. 1981. Mutants of yeast defective in sucrose utilization. *Genetics* **98:** 25–40.

Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, et al. 2012. The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. *Cancer Discov* **2:** 401–404.

Chaban Y, Ezeokonkwo C, Chung WH, Zhang F, Kornberg RD, Maier-Davis B, Lorch Y, Asturias FJ. 2008. Structure of a RSC-nucleosome complex and insights into chromatin remodeling. *Nat Struct Mol Biol* **15:** 1272–1277.

Chai B, Huang J, Cairns BR, Laurent BC. 2005. Distinct roles for the RSC and Swi/Snf ATP-dependent chromatin remodelers in DNA double-strand break repair. *Genes Dev* **19:** 1656–1661.

Chalkley GE, Moshkin YM, Langenberg K, Bezstarosti K, Blastyak A, Gyurkovics H, Demmers JA, Verrijzer CP. 2008. The transcriptional coactivator SAYP is a trithorax group signature subunit of the PBAP chromatin remodeling complex. *Mol Cell Biol* **28:** 2920–2929.

Chandler RL, Damrauer JS, Raab JR, Schisler JC, Wilkerson MD, Didion JP, Starmer J, Serber D, Yee D, Xiong J, et al. 2015. Coexistent ARID1A–PIK3CA mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signalling. *Nat Commun* **6:** 6118.

Chevenet F, Brun C, Banuls AL, Jacq B, Christen R. 2006. TreeDyn: Towards dynamic graphics and annotations for analyses of trees. *BMC Bioinformatics* **7:** 439.

Clapier CR, Cairns BR. 2009. The biology of chromatin remodeling complexes. *Annu Rev Biochem* **78:** 273–304.

Collins RT, Furukawa T, Tanese N, Treisman JE. 1999. Osa associates with the Brahma chromatin remodeling complex and promotes the activation of some target genes. *EMBO J* **18:** 7029–7040.

Corona DF, Armstrong JA, Tamkun JW. 2004. Genetic and cytological analysis of *Drosophila* chromatin-remodeling factors. *Methods Enzymol* **377:** 70–85.

Crew AJ, Clark J, Fisher C, Gill S, Grimer R, Chand A, Shipley J, Gusterson BA, Cooper CS. 1995. Fusion of *SYT* to two genes, *SSX1* and *SSX2*, encoding proteins with homology to the Kruppel-associated box in human synovial sarcoma. *EMBO J* **14:** 2333–2340.

Crosby MA, Miller C, Alon T, Watson KL, Verrijzer CP, Goldman-Levi R, Zak NB. 1999. The *trithorax* group gene *moira* encodes a Brahma-associated putative chromatin-remodeling factor in *Drosophila melanogaster*. *Mol Cell Biol* **19:** 1159–1170.

Davoli T, Xu AW, Mengwasser KE, Sack LM, Yoon JC, Park PJ, Elledge SJ. 2013. Cumulative haploinsufficiency and triplosensitivity drive aneuploidy patterns and shape the cancer genome. *Cell* **155:** 948–962.

Dechassa ML, Zhang B, Horowitz-Scherer R, Persinger J, Woodcock CL, Peterson CL, Bartholomew B. 2008. Architecture of the SWI/SNF-nucleosome complex. *Mol Cell Biol* **28:** 6010–6021.

Deciphering Developmental Disorders Study. 2015. Large-scale discovery of novel genetic causes of developmental disorders. *Nature* **519:** 223–228.

Dhillon N, Raab J, Guzzo J, Szyjka SJ, Gangadharan S, Aparicio OM, Andrews B, Kamakaka RT. 2009. DNA polymerase epsilon, acetylases and remodellers cooperate to form a specialized chromatin structure at a tRNA insulator. *EMBO J* **28:** 2583–2600.

Ding L, Kim M, Kanchi KL, Dees ND, Lu C, Griffith M, Fenstermacher D, Sung H, Miller CA, Goetz B, et al. 2014. Clonal architectures and driver mutations in metastatic melanomas. *PLoS ONE* **9:** e111153.

Dixon JR, Selvaraj S, Yue F, Kim A, Li Y, Shen Y, Hu M, Liu JS, Ren B. 2012. Topological domains in mammalian genomes identified by analysis of chromatin interactions. *Nature* **485:** 376–380.

Dowen JM, Fan ZP, Hnisz D, Ren G, Abraham BJ, Zhang LN, Weintraub AS, Schuijers J, Lee TI, Zhao K, et al. 2014. Control of cell identity genes occurs in insulated neighborhoods in mammalian chromosomes. *Cell* **159:** 374–387.

Dror V, Winston F. 2004. The Swi/Snf chromatin remodeling complex is required for ribosomal DNA and telomeric silencing in *Saccharomyces cerevisiae*. *Mol Cell Biol* **24:** 8227–8235.

Dunaief JL, Strober BE, Guha S, Khavari PA, Alin K, Luban J, Begemann M, Crabtree GR, Goff SP. 1994. The retinoblastoma protein and BRG1 form a complex and cooperate to induce cell cycle arrest. *Cell* **79:** 119–130.

Durr H, Korner C, Muller M, Hickmann V, Hopfner KP. 2005. X-ray structures of the *Sulfolobus solfataricus* SWI2/SNF2 ATPase core and its complex with DNA. *Cell* **121:** 363–373.

Dykhuizen EC, Hargreaves DC, Miller EL, Cui K, Korshunov A, Kool M, Pfister S, Cho YJ, Zhao K, Crabtree GR. 2013. BAF complexes facilitate decatenation of DNA by topoisomerase IIα. *Nature* **497:** 624–627.

Estruch F, Carlson M. 1990. *SNF6* encodes a nuclear protein that is required for expression of many genes in *Saccharomyces cerevisiae*. *Mol Cell Biol* **10:** 2544–2553.

Euskirchen GM, Auerbach RK, Davidov E, Gianoulis TA, Zhong G, Rozowsky J, Bhardwaj N, Gerstein MB, Snyder M. 2011. Diverse roles and interactions of the SWI/SNF chromatin remodeling complex revealed using global approaches. *PLoS Genet* **7:** e1002008.

Fairman-Williams ME, Guenther UP, Jankowsky E. 2010. SF1 and SF2 helicases: Family matters. *Curr Opin Struct Biol* **20:** 313–324.

Fillmore CM, Xu C, Desai PT, Berry JM, Rowbotham SP, Lin YJ, Zhang H, Marquez VE, Hammerman PS, Wong KK, et al. 2015. EZH2 inhibition sensitizes *BRG1* and *EGFR* mutant lung tumours to TopoII inhibitors. *Nature* **520:** 239–242.

Fujimoto A, Furuta M, Shiraishi Y, Gotoh K, Kawakami Y, Arihiro K, Nakamura T, Ueno M, Ariizumi S, Nguyen HH, et al. 2015. Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. *Nat Commun* **6:** 6120.

Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, et al. 2013. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal* **6:** pl1.

Gerhold CB, Hauer MH, Gasser SM. 2015. INO80-C and SWR-C: Guardians of the genome. *J Mol Biol* **427:** 637–651.

Gerlinger M, Horswell S, Larkin J, Rowan AJ, Salm MP, Varela I, Fisher R, McGranahan N, Matthews N, Santos CR, et al. 2014. Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing. *Nat Genet* **46:** 225–233.

Gong F, Fahy D, Smerdon MJ. 2006. Rad4-Rad23 interaction with SWI/SNF links ATP-dependent chromatin remodeling with nucleotide excision repair. *Nat Struct Mol Biol* **13:** 902–907.

Gui Y, Guo G, Huang Y, Hu X, Tang A, Gao S, Wu R, Chen C, Li X, Zhou L, et al. 2011. Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder. *Nat Genet* **43:** 875–878.

Hartley PD, Madhani HD. 2009. Mechanisms that specify promoter nucleosome location and identity. *Cell* **137:** 445–458.

He J, Xuan T, Xin T, An H, Wang J, Zhao G, Li M. 2014. Evidence for chromatin-remodeling complex PBAP-controlled maintenance of the *Drosophila* ovarian germline stem cells. *PLoS ONE* **9:** e103473.

Hedges SB, Dudley J, Kumar S. 2006. TimeTree: A public knowledge-base of divergence times among organisms. *Bioinformatics* **22:** 2971–2972.

Helming KC, Wang X, Wilson BG, Vazquez F, Haswell JR, Manchester HE, Kim Y, Kryukov GV, Ghandi M. 2014. ARID1B is a specific vulnerability in *ARID1A*-mutant cancers. *Nat Med* **20:** 251–254.

Ho L, Crabtree GR. 2010. Chromatin remodelling during development. *Nature* **463:** 474–484.

Ho L, Jothi R, Ronan JL, Cui K, Zhao K, Crabtree GR. 2009a. An embryonic stem cell chromatin remodeling complex, esBAF, is an essential component of the core pluripotency transcriptional network. *Proc Natl Acad Sci* **106:** 5187–5191.

Ho L, Ronan JL, Wu J, Staahl BT, Chen L, Kuo A, Lessard J, Nesvizhskii AI, Ranish J, Crabtree GR. 2009b. An embryonic stem cell chromatin remodeling complex, esBAF, is essential for embryonic stem cell self-renewal and pluripotency. *Proc Natl Acad Sci* **106:** 5181–5186.

Ho L, Miller EL, Ronan JL, Ho WQ, Jothi R, Crabtree GR. 2011. esBAF facilitates pluripotency by conditioning the genome for LIF/STAT3 signalling and by regulating polycomb function. *Nat Cell Biol* **13:** 903–913.

Hodis E, Watson IR, Kryukov GV, Arold ST, Imielinski M, Theurillat JP, Nickerson E, Auclair D, Li L, Place C, et al. 2012. A landscape of driver mutations in melanoma. *Cell* **150:** 251–263.

Hsu JM, Huang J, Meluh PB, Laurent BC. 2003. The yeast RSC chromatin-remodeling complex is required for kinetochore function in chromosome segregation. *Mol Cell Biol* **23:** 3202–3215.

Ibragimova I, Maradeo ME, Dulaimi E, Cairns P. 2013. Aberrant promoter hypermethylation of *PBRM1*, *BAP1*, *SETD2*, *KDM6A* and other chromatin-modifying genes is absent or rare in clear cell RCC. *Epigenetics* **8:** 486–493.

Imielinski M, Berger AH, Hammerman PS, Hernandez B, Pugh TJ, Hodis E, Cho J, Suh J, Capelletti M, Sivachenko A, et al. 2012. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell* **150:** 1107–1120.

Jagani Z, Mora-Blanco EL, Sansam CG, McKenna ES, Wilson B, Chen D, Klekota J, Tamayo P, Nguyen PT, Tolstorukov M, et al. 2010. Loss of the tumor suppressor Snf5 leads to aberrant activation of the Hedgehog–Gli pathway. *Nat Med* **16:** 1429–1433.

Jahromi MS, Putnam AR, Druzgal C, Wright J, Spraker-Perlman H, Kinsey M, Zhou H, Boucher KM, Randall RL, Jones KB, et al. 2012. Molecular inversion probe analysis detects novel copy number alterations in Ewing sarcoma. *Cancer Genet* **205:** 391–404.

Jankowsky E, Fairman ME. 2007. RNA helicases—One fold for many functions. *Curr Opin Struct Biol* **17:** 316–324.

Jelinic P, Mueller JJ, Olvera N, Dao F, Scott SN, Shah R, Gao J, Schultz N, Gonen M, Soslow RA, et al. 2014. Recurrent *SMARCA4* mutations in small cell carcinoma of the ovary. *Nat Genet* **46:** 424–426.

Ji X, Dadon DB, Powell BE, Fan ZP, Borges-Rivera D, Shachar S, Weintraub AS, Hnisz D, Pegoraro G, Lee TI, et al. 2015. 3D chromosome regulatory landscape of human pluripotent cells. *Cell Stem Cell* **18:** 262–275.

Jiao Y, Pawlik TM, Anders RA, Selaru FM, Streppel MM, Lucas DJ, Niknafs N, Guthrie VB, Maitra A, Argani P, et al. 2013. Exome sequencing identifies frequent inactivating mutations in *BAP1*, *ARID1A* and *PBRM1* in intrahepatic cholangiocarcinomas. *Nat Genet* **45:** 1470–1473.

Jones S, Wang TL, Shih Ie M, Mao TL, Nakayama K, Roden R, Glas R, Slamon D, Diaz LA Jr, Vogelstein B, et al. 2010. Frequent mutations of chromatin remodeling gene

ARID1A in ovarian clear cell carcinoma. *Science* **330:** 228–231.

Kadoch C, Crabtree GR. 2013. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. *Cell* **153:** 71–85.

Kadoch C, Hargreaves DC, Hodges C, Elias L, Ho L, Ranish J, Crabtree GR. 2013. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat Genet* **45:** 592–601.

Kaeser MD, Aslanian A, Dong MQ, Yates JR III, Emerson BM. 2008. BRD7, a novel PBAF-specific SWI/SNF subunit, is required for target gene activation and repression in embryonic stem cells. *J Biol Chem* **283:** 32254–32263.

Kagey MH, Newman JJ, Bilodeau S, Zhan Y, Orlando DA, van Berkum NL, Ebmeier CC, Goossens J, Rahl PB, Levine SS, et al. 2010. Mediator and cohesin connect gene expression and chromatin architecture. *Nature* **467:** 430–435.

Kakarougkas A, Ismail A, Chambers AL, Riballo E, Herbert AD, Kunzel J, Lobrich M, Jeggo PA, Downs JA. 2014. Requirement for PBAF in transcriptional repression and repair at DNA breaks in actively transcribed regions of chromatin. *Mol Cell* **55:** 723–732.

Kal AJ, Mahmoudi T, Zak NB, Verrijzer CP. 2000. The *Drosophila* Brahma complex is an essential coactivator for the *trithorax* group protein zeste. *Genes Dev* **14:** 1058–1071.

Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, et al. 2013. Integrated genomic characterization of endometrial carcinoma. *Nature* **497:** 67–73.

Kennison JA, Tamkun JW. 1988. Dosage-dependent modifiers of polycomb and antennapedia mutations in *Drosophila*. *Proc Natl Acad Sci* **85:** 8136–8140.

Khavari PA, Peterson CL, Tamkun JW, Mendel DB, Crabtree GR. 1993. BRG1 contains a conserved domain of the *SWI2/SNF2* family necessary for normal mitotic growth and transcription. *Nature* **366:** 170–174.

Kia SK, Gorski MM, Giannakopoulos S, Verrijzer CP. 2008. SWI/SNF mediates polycomb eviction and epigenetic reprogramming of the *INK4b-ARF-INK4a* locus. *Mol Cell Biol* **28:** 3457–3464.

Kim KH, Kim W, Howard TP, Vazquez F, Tsherniak A, Wu JN, Wang W, Haswell JR, Walensky LD, Hahn WC, et al. 2015. SWI/SNF-mutant cancers depend on catalytic and non-catalytic activity of EZH2. *Nat Med* **21:** 1491–1496.

Kingston RE, Tamkun JW. 2014. Transcriptional regulation by trithorax-group proteins. *Cold Spring Harb Perspect Biol* **6:** a019349.

Kirkland JG, Raab JR, Kamakaka RT. 2013. TFIIIC bound DNA elements in nuclear organization and insulation. *Biochim Biophys Acta* **1829:** 418–424.

Krasteva V, Buscarlet M, Diaz-Tellez A, Bernard MA, Crabtree GR, Lessard JA. 2012. The BAF53a subunit of SWI/SNF-like BAF complexes is essential for hemopoietic stem cell function. *Blood* **120:** 4720–4732.

Kruger W, Peterson CL, Sil A, Coburn C, Arents G, Moudrianakis EN, Herskowitz I. 1995. Amino acid substitutions in the structured domains of histones H3 and H4 partially relieve the requirement of the yeast SWI/SNF complex for transcription. *Genes Dev* **9:** 2770–2779.

Laurent BC, Treich I, Carlson M. 1993. The yeast SNF2/SWI2 protein has DNA-stimulated ATPase activity required for transcriptional activation. *Genes Dev* **7:** 583–591.

Lawrence MS, Stojanov P, Mermel CH, Robinson JT, Garraway LA, Golub TR, Meyerson M, Gabriel SB, Lander ES, Getz G. 2014. Discovery and saturation analysis of cancer genes across 21 tumour types. *Nature* **505:** 495–501.

Lee HS, Park JH, Kim SJ, Kwon SJ, Kwon J. 2010. A cooperative activation loop among SWI/SNF, γ-H2AX and H3 acetylation for DNA double-strand break repair. *EMBO J* **29:** 1434–1445.

Lee RS, Stewart C, Carter SL, Ambrogio L, Cibulskis K, Sougnez C, Lawrence MS, Auclair D, Mora J, Golub TR, et al. 2012. A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. *J Clin Invest* **122:** 2983–2988.

Lee JJ, Sholl LM, Lindeman NI, Granter SR, Laga AC, Shivdasani P, Chin G, Luke JJ, Ott PA, Hodi FS, et al. 2015. Targeted next-generation sequencing reveals high frequency of mutations in epigenetic regulators across treatment-naive patient melanomas. *Clin Epigenetics* **7:** 59.

Le Loarer F, Watson S, Pierron G, de Montpreville VT, Ballet S, Firmin N, Auguste A, Pissaloux D, Boyault S, Paindavoine S, et al. 2015. *SMARCA4* inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. *Nat Genet* **47:** 1200–1205.

Lemon B, Inouye C, King DS, Tjian R. 2001. Selectivity of chromatin-remodelling cofactors for ligand-activated transcription. *Nature* **414:** 924–928.

Leschziner AE, Lemon B, Tjian R, Nogales E. 2005. Structural studies of the human PBAF chromatin-remodeling complex. *Structure* **13:** 267–275.

Leschziner AE, Saha A, Wittmeyer J, Zhang Y, Bustamante C, Cairns BR, Nogales E. 2007. Conformational flexibility in the chromatin remodeler RSC observed by electron microscopy and the orthogonal tilt reconstruction method. *Proc Natl Acad Sci* **104:** 4913–4918.

Lessard J, Wu JI, Ranish JA, Wan M, Winslow MM, Staahl BT, Wu H, Aebersold R, Graef IA, Crabtree GR. 2007. An essential switch in subunit composition of a chromatin remodeling complex during neural development. *Neuron* **55:** 201–215.

Li XS, Trojer P, Matsumura T, Treisman JE, Tanese N. 2010. Mammalian SWI/SNF—A subunit BAF250/ARID1 is an E3 ubiquitin ligase that targets histone H2B. *Mol Cell Biol* **30:** 1673–1688.

Li M, Zhao H, Zhang X, Wood LD, Anders RA, Choti MA, Pawlik TM, Daniel HD, Kannangai R, Offerhaus GJ, et al. 2011. Inactivating mutations of the chromatin remodeling gene *ARID2* in hepatocellular carcinoma. *Nat Genet* **43:** 828–829.

Li YY, Hanna GJ, Laga AC, Haddad RI, Lorch JH, Hammerman PS. 2015. Genomic analysis of metastatic cutaneous squamous cell carcinoma. *Clin Cancer Res* **21:** 1447–1456.

Lickert H, Takeuchi JK, Von Both I, Walls JR, McAuliffe F, Adamson SL, Henkelman RM, Wrana JL, Rossant J, Bruneau BG. 2004. Baf60c is essential for function of BAF

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

chromatin remodelling complexes in heart development. *Nature* **432:** 107–112.

Lippman Z, Gendrel AV, Black M, Vaughn MW, Dedhia N, McCombie WR, Lavine K, Mittal V, May B, Kasschau KD, et al. 2004. Role of transposable elements in heterochromatin and epigenetic control. *Nature* **430:** 471–476.

Liu R, Liu H, Chen X, Kirby M, Brown PO, Zhao K. 2001. Regulation of CSF1 promoter by the SWI/SNF-like BAF complex. *Cell* **106:** 309–318.

Lunyak VV, Prefontaine GG, Nunez E, Cramer T, Ju BG, Ohgi KA, Hutt K, Roy R, Garcia-Diaz A, Zhu X, et al. 2007. Developmentally regulated activation of a SINE B2 repeat as a domain boundary in organogenesis. *Science* **317:** 248–251.

Manceau G, Letouze E, Guichard C, Didelot A, Cazes A, Corte H, Fabre E, Pallier K, Imbeaud S, Le Pimpec-Barthes F, et al. 2013. Recurrent inactivating mutations of *ARID2* in non-small cell lung carcinoma. *Int J Cancer* **132:** 2217–2221.

Manning BJ, Peterson CL. 2014. Direct interactions promote eviction of the Sir3 heterochromatin protein by the SWI/SNF chromatin remodeling enzyme. *Proc Natl Acad Sci* **111:** 17827–17832.

McKenna ES, Roberts CW. 2009. Epigenetics and cancer without genomic instability. *Cell Cycle* **8:** 23–26.

McKenna ES, Sansam CG, Cho YJ, Greulich H, Evans JA, Thom CS, Moreau LA, Biegel JA, Pomeroy SL, Roberts CW. 2008. Loss of the epigenetic tumor suppressor SNF5 leads to cancer without genomic instability. *Mol Cell Biol* **28:** 6223–6233.

Medina PP, Sanchez-Cespedes M. 2008. Involvement of the chromatin-remodeling factor *BRG1/SMARCA4* in human cancer. *Epigenetics* **3:** 64–68.

Medina PP, Carretero J, Fraga MF, Esteller M, Sidransky D, Sanchez-Cespedes M. 2004. Genetic and epigenetic screening for gene alterations of the chromatin-remodeling factor, *SMARCA4/BRG1*, in lung tumors. *Genes Chromosomes Cancer* **41:** 170–177.

Medina PP, Romero OA, Kohno T, Montuenga LM, Pio R, Yokota J, Sanchez-Cespedes M. 2008. Frequent *BRG1/SMARCA4*-inactivating mutations in human lung cancer cell lines. *Hum Mutat* **29:** 617–622.

Middeljans E, Wan X, Jansen PW, Sharma V, Stunnenberg HG, Logie C. 2012. SS18 together with animal-specific factors defines human BAF-type SWI/SNF complexes. *PLoS ONE* **7:** e33834.

Mohrmann L, Langenberg K, Krijgsveld J, Kal AJ, Heck AJ, Verrijzer CP. 2004. Differential targeting of two distinct SWI/SNF-related *Drosophila* chromatin-remodeling complexes. *Mol Cell Biol* **24:** 3077–3088.

Molnar C, Lopez-Varea A, Hernandez R, de Celis JF. 2006. A gain-of-function screen identifying genes required for vein formation in the *Drosophila melanogaster* wing. *Genetics* **174:** 1635–1659.

Mora-Blanco EL, Mishina Y, Tillman EJ, Cho YJ, Thom CS, Pomeroy SL, Shao W, Roberts CW. 2014. Activation of β-catenin/TCF targets following loss of the tumor suppressor SNF5. *Oncogene* **33:** 933–938.

Moshkin YM, Mohrmann L, van Ijcken WF, Verrijzer CP. 2007. Functional differentiation of SWI/SNF remodelers in transcription and cell cycle control. *Mol Cell Biol* **27:** 651–661.

Naka N, Takenaka S, Araki N, Miwa T, Hashimoto N, Yoshioka K, Joyama S, Hamada K, Tsukamoto Y, Tomita Y, et al. 2010. Synovial sarcoma is a stem cell malignancy. *Stem Cells* **28:** 1119–1131.

Narlikar GJ, Sundaramoorthy R, Owen-Hughes T. 2013. Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes. *Cell* **154:** 490–503.

Neigeborn L, Carlson M. 1984. Genes affecting the regulation of *SUC2* gene expression by glucose repression in *Saccharomyces cerevisiae*. *Genetics* **108:** 845–858.

Neigeborn L, Carlson M. 1987. Mutations causing constitutive invertase synthesis in yeast: Genetic interactions with *snf* mutations. *Genetics* **115:** 247–253.

Niimi A, Chambers AL, Downs JA, Lehmann AR. 2012. A role for chromatin remodellers in replication of damaged DNA. *Nucleic Acids Res* **40:** 7393–7403.

Niimi A, Hopkins SR, Downs JA, Masutani C. 2015. The BAH domain of BAF180 is required for PCNA ubiquitination. *Mutat Res* **779:** 16–23.

Ogiwara H, Ui A, Otsuka A, Satoh H, Yokomi I, Nakajima S, Yasui A, Yokota J, Kohno T. 2011. Histone acetylation by CBP and p300 at double-strand break sites facilitates SWI/SNF chromatin remodeling and the recruitment of non-homologous end joining factors. *Oncogene* **30:** 2135–2146.

Oki M, Valenzuela L, Chiba T, Ito T, Kamakaka RT. 2004. Barrier proteins remodel and modify chromatin to restrict silenced domains. *Mol Cell Biol* **24:** 1956–1967.

Olave I, Wang W, Xue Y, Kuo A, Crabtree GR. 2002. Identification of a polymorphic, neuron-specific chromatin remodeling complex. *Genes Dev* **16:** 2509–2517.

Oruetxebarria I, Venturini F, Kekarainen T, Houweling A, Zuijderduijn LM, Mohd-Sarip A, Vries RG, Hoeben RC, Verrijzer CP. 2004. $P16^{INK4a}$ is required for hSNF5 chromatin remodeler-induced cellular senescence in malignant rhabdoid tumor cells. *J Biol Chem* **279:** 3807–3816.

Pang B, de Jong J, Qiao X, Wessels LF, Neefjes J. 2015. Chemical profiling of the genome with anti-cancer drugs defines target specificities. *Nat Chem Biol* **11:** 472–480.

Papoulas O, Beek SJ, Moseley SL, McCallum CM, Sarte M, Shearn A, Tamkun JW. 1998. The *Drosophila* trithorax group proteins BRM, ASH1 and ASH2 are subunits of distinct protein complexes. *Development* **125:** 3955–3966.

Parnell TJ, Huff JT, Cairns BR. 2008. RSC regulates nucleosome positioning at Pol II genes and density at Pol III genes. *EMBO J* **27:** 100–110.

Patrick KL, Ryan CJ, Xu J, Lipp JJ, Nissen KE, Roguev A, Shales M, Krogan NJ, Guthrie C. 2015. Genetic interaction mapping reveals a role for the SWI/SNF nucleosome remodeler in spliceosome activation in fission yeast. *PLoS Genet* **11:** e1005074.

Peng G, Yim EK, Dai H, Jackson AP, Burgt I, Pan MR, Hu R, Li K, Lin SY. 2009. BRIT1/MCPH1 links chromatin remodelling to DNA damage response. *Nat Cell Biol* **11:** 865–872.

Peterson CL, Herskowitz I. 1992. Characterization of the yeast *SWI1*, *SWI2*, and *SWI3* genes, which encode a global activator of transcription. *Cell* **68:** 573–583.

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Peterson CL, Dingwall A, Scott MP. 1994. Five *SWI/SNF* gene products are components of a large multisubunit complex required for transcriptional enhancement. *Proc Natl Acad Sci* **91:** 2905–2908.

Peterson CL, Zhao Y, Chait BT. 1998. Subunits of the yeast SWI/SNF complex are members of the actin-related protein (ARP) family. *J Biol Chem* **273:** 23641–23644.

Phelan ML, Sif S, Narlikar GJ, Kingston RE. 1999. Reconstitution of a core chromatin remodeling complex from SWI/SNF subunits. *Mol Cell* **3:** 247–253.

Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, Patel L, Vergara IA, Davicioni E, Erho N, Ghadessi M, et al. 2013. The long noncoding RNA *SChLAP1* promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. *Nat Genet* **45:** 1392–1398.

Pugh TJ, Weeraratne SD, Archer TC, Pomeranz Krummel DA, Auclair D, Bochicchio J, Carneiro MO, Carter SL, Cibulskis K, Erlich RL, et al. 2012. Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. *Nature* **488:** 106–110.

Qi W, Wang R, Chen H, Wang X, Xiao T, Boldogh I, Ba X, Han L, Zeng X. 2015. BRG1 promotes the repair of DNA double-strand breaks by facilitating the replacement of RPA with RAD51. *J Cell Sci* **128:** 317–330.

Raab JR, Resnick S, Magnuson T. 2015. Genome-wide transcriptional regulation mediated by biochemically distinct SWI/SNF complexes. *PLoS Genet* **11:** e1005748.

Rada-Iglesias A, Bajpai R, Swigut T, Brugmann SA, Flynn RA, Wysocka J. 2011. A unique chromatin signature uncovers early developmental enhancers in humans. *Nature* **470:** 279–283.

Ramos P, Karnezis AN, Craig DW, Sekulic A, Russell ML, Hendricks WP, Corneveaux JJ, Barrett MT, Shumansky K, Yang Y, et al. 2014. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in *SMARCA4*. *Nat Genet* **46:** 427–429.

Rando OJ, Zhao K, Janmey P, Crabtree GR. 2002. Phosphatidylinositol-dependent actin filament binding by the SWI/SNF-like BAF chromatin remodeling complex. *Proc Natl Acad Sci* **99:** 2824–2829.

Reinhold WC, Sunshine M, Liu H, Varma S, Kohn KW, Morris J, Doroshow J, Pommier Y. 2012. CellMiner: A web-based suite of genomic and pharmacologic tools to explore transcript and drug patterns in the NCI-60 cell line set. *Cancer Res* **72:** 3499–3511.

Reisman DN, Strobeck MW, Betz BL, Sciariotta J, Funkhouser W Jr, Murchardt C, Yaniv M, Sherman LS, Knudsen ES, Weissman BE. 2002. Concomitant down-regulation of BRM and BRG1 in human tumor cell lines: Differential effects on RB-mediated growth arrest vs CD44 expression. *Oncogene* **21:** 1196–1207.

Rendina R, Strangi A, Avallone B, Giordano E. 2010. Bap170, a subunit of the *Drosophila* PBAP chromatin remodeling complex, negatively regulates the EGFR signaling. *Genetics* **186:** 167–181.

Richmond E, Peterson CL. 1996. Functional analysis of the DNA-stimulated ATPase domain of yeast SWI2/SNF2. *Nucleic Acids Res* **24:** 3685–3692.

Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, et al. 2015. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* **348:** 124–128.

Roberts CW, Biegel JA. 2009. The role of SMARCB1/INI1 in development of rhabdoid tumor. *Cancer Biol Ther* **8:** 412–416.

Roberts CW, Galusha SA, McMenamin ME, Fletcher CD, Orkin SH. 2000. Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. *Proc Natl Acad Sci* **97:** 13796–13800.

Santen GW, Aten E, Sun Y, Almomani R, Gilissen C, Nielsen M, Kant SG, Snoeck IN, Peeters EA, Hilhorst-Hofstee Y, et al. 2012. Mutations in SWI/SNF chromatin remodeling complex gene *ARID1B* cause Coffin–Siris syndrome. *Nat Genet* **44:** 379–380.

Sausen M, Leary RJ, Jones S, Wu J, Reynolds CP, Liu X, Blackford A, Parmigiani G, Diaz LA Jr, Papadopoulos N, et al. 2013. Integrated genomic analyses identify *ARID1A* and *ARID1B* alterations in the childhood cancer neuroblastoma. *Nat Genet* **45:** 12–17.

Schnitzler GR, Cheung CL, Hafner JH, Saurin AJ, Kingston RE, Lieber CM. 2001. Direct imaging of human SWI/SNF-remodeled mono- and polynucleosomes by atomic force microscopy employing carbon nanotube tips. *Mol Cell Biol* **21:** 8504–8511.

Schoenfelder S, Sugar R, Dimond A, Javierre BM, Armstrong H, Mifsud B, Dimitrova E, Matheson L, Tavares-Cadete F, Furlan-Magaril M, et al. 2015. Polycomb repressive complex PRC1 spatially constrains the mouse embryonic stem cell genome. *Nat Genet* **47:** 1179–1186.

Schubert HL, Wittmeyer J, Kasten MM, Hinata K, Rawling DC, Heroux A, Cairns BR, Hill CP. 2013. Structure of an actin-related subcomplex of the SWI/SNF chromatin remodeler. *Proc Natl Acad Sci* **110:** 3345–3350.

Shain AH, Pollack JR. 2013. The spectrum of SWI/SNF mutations, ubiquitous in human cancers. *PLoS ONE* **8:** e55119.

Shain AH, Garrido M, Botton T, Talevich E, Yeh I, Sanborn JZ, Chung J, Wang NJ, Kakavand H, Mann GJ, et al. 2015. Exome sequencing of desmoplastic melanoma identifies recurrent *NFKBIE* promoter mutations and diverse activating mutations in the MAPK pathway. *Nat Genet* **47:** 1194–1199.

Shaver S, Casas-Mollano JA, Cerny RL, Cerutti H. 2010. Origin of the polycomb repressive complex 2 and gene silencing by an E(z) homolog in the unicellular alga *Chlamydomonas*. *Epigenetics* **5:** 301–312.

Shen X, Ranallo R, Choi E, Wu C. 2003. Involvement of actin-related proteins in ATP-dependent chromatin remodeling. *Mol Cell* **12:** 147–155.

Shi J, Wang E, Milazzo JP, Wang Z, Kinney JB, Vakoc CR. 2015. Discovery of cancer drug targets by CRISPR-Cas9 screening of protein domains. *Nat Biotechnol* **33:** 661–667.

Shim EY, Ma JL, Oum JH, Yanez Y, Lee SE. 2005. The yeast chromatin remodeler RSC complex facilitates end joining repair of DNA double-strand breaks. *Mol Cell Biol* **25:** 3934–3944.

Simon JA, Tamkun JW. 2002. Programming off and on states in chromatin: Mechanisms of polycomb and trithorax group complexes. *Curr Opin Genet Dev* **12:** 210–218.

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Singhal N, Graumann J, Wu G, Arauzo-Bravo MJ, Han DW, Greber B, Gentile L, Mann M, Scholer HR. 2010. Chromatin-remodeling components of the BAF complex facilitate reprogramming. *Cell* **141:** 943–955.

Skene PJ, Hernandez AE, Groudine M, Henikoff S. 2014. The nucleosomal barrier to promoter escape by RNA polymerase II is overcome by the chromatin remodeler Chd1. *eLife* **3:** e02042.

Smith CL, Peterson CL. 2005. A conserved Swi2/Snf2 ATPase motif couples ATP hydrolysis to chromatin remodeling. *Mol Cell Biol* **25:** 5880–5892.

Smith CL, Horowitz-Scherer R, Flanagan JF, Woodcock CL, Peterson CL. 2003. Structural analysis of the yeast SWI/SNF chromatin remodeling complex. *Nat Struct Biol* **10:** 141–145.

Sperling AS, Jeong KS, Kitada T, Grunstein M. 2011. Topoisomerase II binds nucleosome-free DNA and acts redundantly with topoisomerase I to enhance recruitment of RNA Pol II in budding yeast. *Proc Natl Acad Sci* **108:** 12693–12698.

Srivas R, Costelloe T, Carvunis AR, Sarkar S, Malta E, Sun SM, Pool M, Licon K, van Welsem T, van Leeuwen F, et al. 2013. A UV-induced genetic network links the RSC complex to nucleotide excision repair and shows dose-dependent rewiring. *Cell Rep* **5:** 1714–1724.

Staahl BT, Tang J, Wu W, Sun A, Gitler AD, Yoo AS, Crabtree GR. 2013. Kinetic analysis of npBAF to nBAF switching reveals exchange of SS18 with CREST and integration with neural developmental pathways. *J Neurosci* **33:** 10348–10361.

Stern M, Jensen R, Herskowitz I. 1984. Five *SWI* genes are required for expression of the *HO* gene in yeast. *J Mol Biol* **178:** 853–868.

Sternberg PW, Stern MJ, Clark I, Herskowitz I. 1987. Activation of the yeast *HO* gene by release from multiple negative controls. *Cell* **48:** 567–577.

Szerlong H, Saha A, Cairns BR. 2003. The nuclear actin-related proteins Arp7 and Arp9: A dimeric module that cooperates with architectural proteins for chromatin remodeling. *EMBO J* **22:** 3175–3187.

Szerlong H, Hinata K, Viswanathan R, Erdjument-Bromage H, Tempst P, Cairns BR. 2008. The HSA domain binds nuclear actin-related proteins to regulate chromatin-remodeling ATPases. *Nat Struct Mol Biol* **15:** 469–476.

Tamkun JW, Deuring R, Scott MP, Kissinger M, Pattatucci AM, Kaufman TC, Kennison JA. 1992. *brahma*: A regulator of *Drosophila* homeotic genes structurally related to the yeast transcriptional activator SNF2/SWI2. *Cell* **68:** 561–572.

Taulli R, Foglizzo V, Morena D, Coda DM, Ala U, Bersani F, Maestro N, Ponzetto C. 2014. Failure to downregulate the BAF53a subunit of the SWI/SNF chromatin remodeling complex contributes to the differentiation block in rhabdomyosarcoma. *Oncogene* **33:** 2354–2362.

Terriente-Felix A, de Celis JF. 2009. Osa, a subunit of the BAP chromatin-remodelling complex, participates in the regulation of gene expression in response to EGFR signalling in the *Drosophila* wing. *Dev Biol* **329:** 350–361.

The Cancer Genome Atlas. 2012a. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* **487:** 330–337.

The Cancer Genome Atlas. 2012b. Comprehensive molecular portraits of human breast tumours. *Nature* **490:** 61–70.

The Cancer Genome Atlas. 2014a. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* **513:** 202–209.

The Cancer Genome Atlas. 2014b. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature* **507:** 315–322.

The Cancer Genome Atlas. 2014c. Comprehensive molecular profiling of lung adenocarcinoma. *Nature* **511:** 543–550.

The Cancer Genome Atlas. 2015. Genomic classification of cutaneous melanoma. *Cell* **161:** 1681–1696.

Thoma NH, Czyzewski BK, Alexeev AA, Mazin AV, Kowalczykowski SC, Pavletich NP. 2005. Structure of the SWI2/SNF2 chromatin-remodeling domain of eukaryotic Rad54. *Nat Struct Mol Biol* **12:** 350–356.

Trouche D, Le Chalony C, Muchardt C, Yaniv M, Kouzarides T. 1997. RB and hbrm cooperate to repress the activation functions of E2F1. *Proc Natl Acad Sci* **94:** 11268–11273.

Tsurusaki Y, Okamoto N, Ohashi H, Kosho T, Imai Y, Hibi-Ko Y, Kaname T, Naritomi K, Kawame H, Wakui K, et al. 2012. Mutations affecting components of the SWI/SNF complex cause Coffin–Siris syndrome. *Nat Genet* **44:** 376–378.

Tyagi A, Ryme J, Brodin D, Ostlund Farrants AK, Visa N. 2009. SWI/SNF associates with nascent pre-mRNPs and regulates alternative pre-mRNA processing. *PLoS Genet* **5:** e1000470.

Varela I, Tarpey P, Raine K, Huang D, Ong CK, Stephens P, Davies H, Jones D, Lin ML, Teague J, et al. 2011. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene *PBRM1* in renal carcinoma. *Nature* **469:** 539–542.

Versteege I, Sevenet N, Lange J, Rousseau-Merck MF, Ambros P, Handgretinger R, Aurias A, Delattre O. 1998. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature* **394:** 203–206.

Vogel-Ciernia A, Matheos DP, Barrett RM, Kramar EA, Azzawi S, Chen Y, Magnan CN, Zeller M, Sylvain A, Haettig J, et al. 2013. The neuron-specific chromatin regulatory subunit BAF53b is necessary for synaptic plasticity and memory. *Nat Neurosci* **16:** 552–561.

Waldholm J, Wang Z, Brodin D, Tyagi A, Yu S, Theopold U, Farrants AK, Visa N. 2011. SWI/SNF regulates the alternative processing of a specific subset of pre-mRNAs in *Drosophila melanogaster*. *BMC Mol Biol* **12:** 46.

Walker JE, Saraste M, Runswick MJ, Gay NJ. 1982. Distantly related sequences in the α- and β-subunits of ATP synthase, myosin, kinases and other ATP-requiring enzymes and a common nucleotide binding fold. *EMBO J* **1:** 945–951.

Wang W, Cote J, Xue Y, Zhou S, Khavari PA, Biggar SR, Muchardt C, Kalpana GV, Goff SP, Yaniv M, et al. 1996a. Purification and biochemical heterogeneity of the mammalian SWI-SNF complex. *EMBO J* **15:** 5370–5382.

Wang W, Xue Y, Zhou S, Kuo A, Cairns BR, Crabtree GR. 1996b. Diversity and specialization of mammalian SWI/SNF complexes. *Genes Dev* **10:** 2117–2130.

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Wang W, Chi T, Xue Y, Zhou S, Kuo A, Crabtree GR. 1998. Architectural DNA binding by a high-mobility-group/kinesin-like subunit in mammalian SWI/SNF-related complexes. *Proc Natl Acad Sci* **95:** 492–498.

Wang K, Kan J, Yuen ST, Shi ST, Chu KM, Law S, Chan TL, Kan Z, Chan AS, Tsui WY, et al. 2011a. Exome sequencing identifies frequent mutation of *ARID1A* in molecular subtypes of gastric cancer. *Nat Genet* **43:** 1219–1223.

Wang X, Werneck MB, Wilson BG, Kim HJ, Kluk MJ, Thom CS, Wischhusen JW, Evans JA, Jesneck JL, Nguyen P, et al. 2011b. TCR-dependent transformation of mature memory phenotype T cells in mice. *J Clin Invest* **121:** 3834–3845.

Wang H, Maurano MT, Qu H, Varley KE, Gertz J, Pauli F, Lee K, Canfield T, Weaver M, Sandstrom R, et al. 2012. Widespread plasticity in CTCF occupancy linked to DNA methylation. *Genome Res* **22:** 1680–1688.

Wang K, Yuen ST, Xu J, Lee SP, Yan HH, Shi ST, Siu HC, Deng S, Chu KM, Law S, et al. 2014. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat Genet* **46:** 573–582.

Wani AH, Boettiger AN, Schorderet P, Ergun A, Munger C, Sadreyev RI, Zhuang X, Kingston RE, Francis NJ. 2016. Chromatin topology is coupled to Polycomb group protein subnuclear organization. *Nat Commun* **7:** 10291.

Watanabe R, Ui A, Kanno S, Ogiwara H, Nagase T, Kohno T, Yasui A. 2014. SWI/SNF factors required for cellular resistance to DNA damage include ARID1A and ARID1B and show interdependent protein stability. *Cancer Res* **74:** 2465–2475.

Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, et al. 2010. *ARID1A* mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med* **363:** 1532–1543.

Wijdeven RH, Pang B, van der Zanden SY, Qiao X, Blomen V, Hoogstraat M, Lips EH, Janssen L, Wessels L, Brummelkamp TR, et al. 2015. Genome-wide identification and characterization of novel factors conferring resistance to topoisomerase II poisons in cancer. *Cancer Res* **75:** 4176–4187.

Wilson BG, Wang X, Shen X, McKenna ES, Lemieux ME, Cho YJ, Koellhoffer EC, Pomeroy SL, Orkin SH, Roberts CW. 2010. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell* **18:** 316–328.

Wilson BG, Helming KC, Wang X, Kim Y, Vazquez F, Jagani Z, Hahn WC, Roberts CW. 2014. Residual complexes containing SMARCA2 (BRM) underlie the oncogenic drive of *SMARCA4* (*BRG1*) mutation. *Mol Cell Biol* **34:** 1136–1144.

Winston F, Carlson M. 1992. Yeast SNF/SWI transcriptional activators and the SPT/SIN chromatin connection. *Trends Genet* **8:** 387–391.

Wollmann P, Cui S, Viswanathan R, Berninghausen O, Wells MN, Moldt M, Witte G, Butryn A, Wendler P, Beckmann R, et al. 2011. Structure and mechanism of the Swi2/Snf2 remodeller Mot1 in complex with its substrate TBP. *Nature* **475:** 403–407.

Wong AK, Shanahan F, Chen Y, Lian L, Ha P, Hendricks K, Ghaffari S, Iliev D, Penn B, Woodland AM, et al. 2000. *BRG1*, a component of the SWI-SNF complex, is mutated in multiple human tumor cell lines. *Cancer Res* **60:** 6171–6177.

Wu JI, Lessard J, Olave IA, Qiu Z, Ghosh A, Graef IA, Crabtree GR. 2007. Regulation of dendritic development by neuron-specific chromatin remodeling complexes. *Neuron* **56:** 94–108.

Xia L, Jaafar L, Cashikar A, Flores-Rozas H. 2007. Identification of genes required for protection from doxorubicin by a genome-wide screen in *Saccharomyces cerevisiae*. *Cancer Res* **67:** 11411–11418.

Xu F, Flowers S, Moran E. 2012. Essential role of ARID2 protein-containing SWI/SNF complex in tissue-specific gene expression. *J Biol Chem* **287:** 5033–5041.

Xue Y, Canman JC, Lee CS, Nie Z, Yang D, Moreno GT, Young MK, Salmon ED, Wang W. 2000. The human SWI/SNF-B chromatin-remodeling complex is related to yeast rsc and localizes at kinetochores of mitotic chromosomes. *Proc Natl Acad Sci* **97:** 13015–13020.

Yan J, Enge M, Whitington T, Dave K, Liu J, Sur I, Schmierer B, Jolma A, Kivioja T, Taipale M, et al. 2013. Transcription factor binding in human cells occurs in dense clusters formed around cohesin anchor sites. *Cell* **154:** 801–813.

Yoo AS, Staahl BT, Chen L, Crabtree GR. 2009. MicroRNA-mediated switching of chromatin-remodelling complexes in neural development. *Nature* **460:** 642–646.

Yoo AS, Sun AX, Li L, Shcheglovitov A, Portmann T, Li Y, Lee-Messer C, Dolmetsch RE, Tsien RW, Crabtree GR. 2011. MicroRNA-mediated conversion of human fibroblasts to neurons. *Nature* **476:** 228–231.

Zhang X, Sun Q, Shan M, Niu M, Liu T, Xia B, Liang X, Wei W, Sun S, Zhang Y, et al. 2013. Promoter hypermethylation of *ARID1A* gene is responsible for its low mRNA expression in many invasive breast cancers. *PLoS ONE* **8:** e53931.

Zhao K, Wang W, Rando OJ, Xue Y, Swiderek K, Kuo A, Crabtree GR. 1998. Rapid and phosphoinositol-dependent binding of the SWI/SNF-like BAF complex to chromatin after T lymphocyte receptor signaling. *Cell* **95:** 625–636.

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

The Many Roles of BAF (mSWI/SNF) and PBAF Complexes in Cancer

Courtney Hodges, Jacob G. Kirkland and Gerald R. Crabtree

Cold Spring Harb Perspect Med published online July 13, 2016