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The Role and Activity of SWI/SNF Chromatin Remodelers

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SWI/SNF ATPases, nucleosome, chromatin, remodeling, transcription factors, development, stimulus response

Abstract

SWITCH deficient SUCROSE NONFERMENTING (SWI/SNF) class chromatin remodeling complexes (CRCs) use the energy derived from ATP hydrolysis to facilitate access of proteins to the genomic DNA for transcription, replication, and DNA repair. Uniquely, SWI/SNF CRCs can both slide the histone octamer along the DNA or eject it from the DNA. Given their ability to change the chromatin status quo, SWI/SNF remodelers are critical for cell fate reprogramming with pioneer and other transcription factors, for responses to environmental challenges, and for disease prevention. Recent cryo-electron microscopy and mass spectrometry approaches have uncovered different subtypes of SWI/SNF complexes with unique properties and functions. At the same time, tethering or rapid depletion and inactivation of SWI/SNF have provided novel insight into SWI/SNF requirements for enhancer activity and into balancing chromatin compaction and accessibility in concert with Polycomb complexes. Given their importance, SWI/SNF recruitment to genomic locations by transcription factors and their biochemical activity is tightly controlled. This review focuses on recent advances in our understanding of SWI/SNF CRCs in animals and plants and discusses the multiple nuclear and biological roles of SWI/SNF CRCs and how SWI/SNF activity is altered by complex subunit composition, posttranslational modifications, and the chromatin context to support proper development and response to extrinsic cues.

Contents

1. INTRODUCTION

Nucleosome: the basic unit of chromatin consisting of 147 bp of DNA wound around an octamer of histones: two H2A-H2B dimers and one H3-H4 tetramer

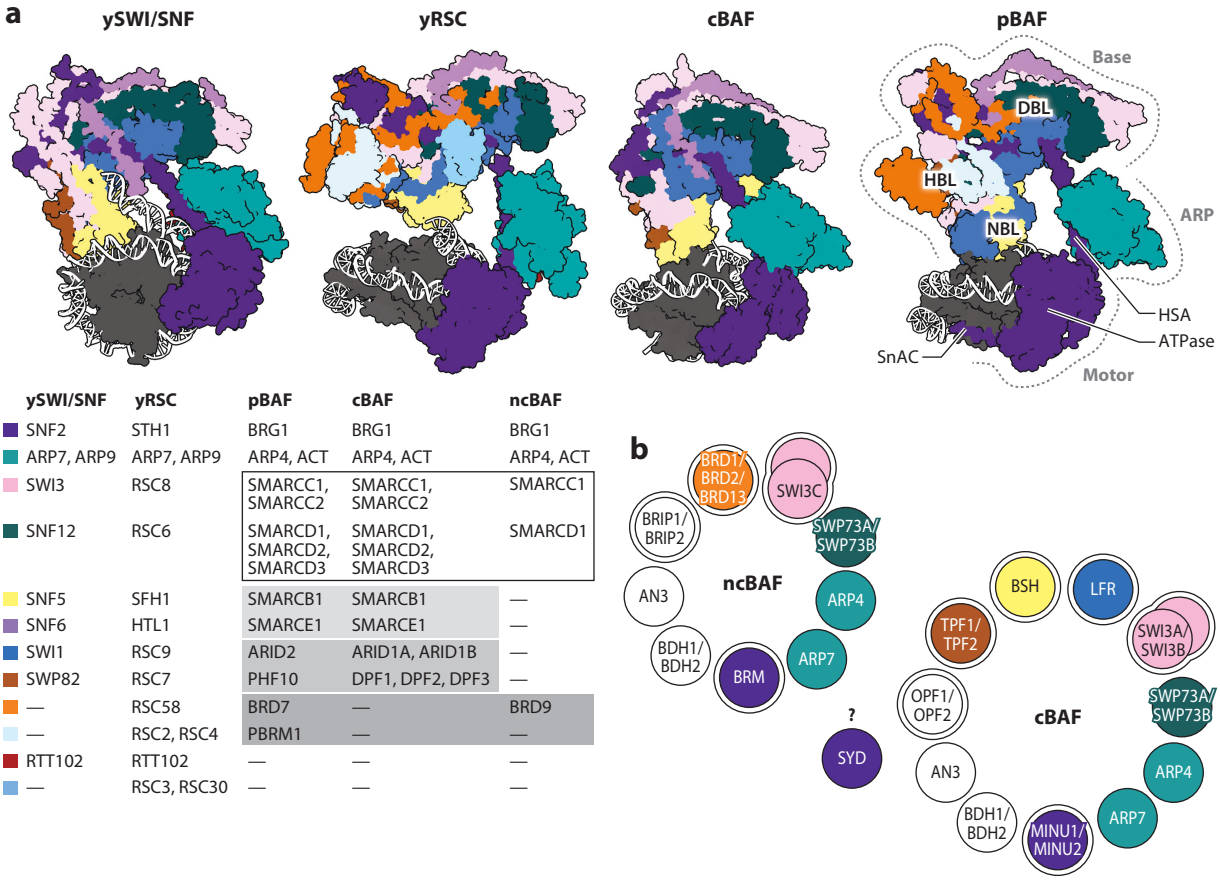
Chromatin Remodeling Complexes (CRCs): conserved multisubunit complexes formed around a central ATPase that modulate DNA accessibility in the context of chromatin

Nucleosomes, DNA wound around histone octamers in chromatin, represent a barrier for protein access to the genome. However, nucleosomes are not static; their occupancy (how frequently a given DNA region is in contact with histones in a population of cells) and nucleosome positioning (the precise location of the histone octamer in a DNA region) can be altered by chromatin remodeling complexes (CRCs). CRCs use the energy derived from ATP hydrolysis to break the largely electrostatic interactions between the positively charged histones and the negatively charged DNA (20). Four main classes of CRCs are found in yeast, animals, and plants: IMITATION SWITCH (ISWI), INOSITOL requiring 80 (INO80), CHROMODOMAIN HELICASE DNA-binding (CHD), and mating type SWITCH deficient SUCROSE NONFERMENTING (SWI/SNF). Among these, SWI/SNF CRCs are unique in that they alter accessibility of the genomic DNA in the context of chromatin not only by sliding the histone octamer along the DNA (i.e., altering nucleosome positioning) but also by ejecting the histone octamer (i.e., reducing nucleosome occupancy) (20). These activities are critical for nuclear processes, from transcription to DNA repair and replication.

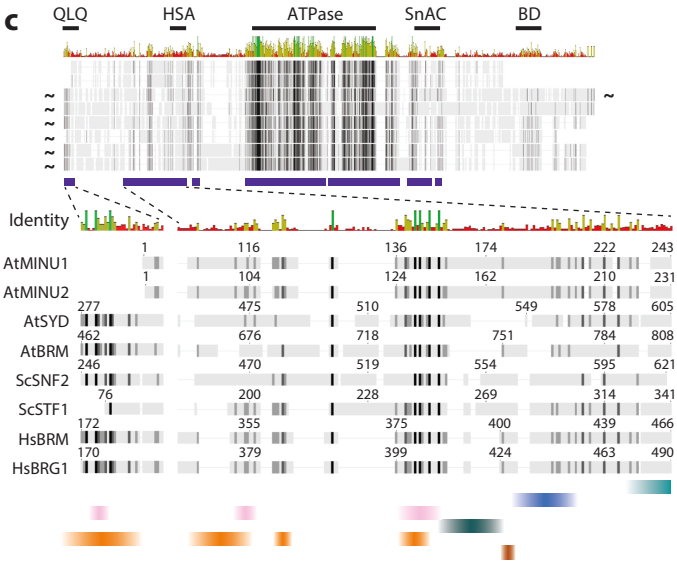
2. SWI/SNF COMPLEX COMPOSITION AND SUBUNITS

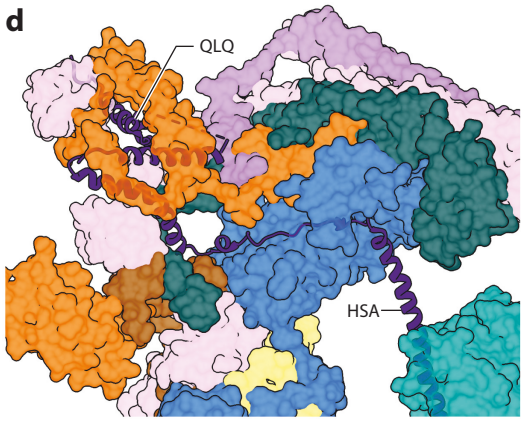
2.1. Three Subtypes of Animal SWI/SNF Complexes

SWI/SNF CRCs are large (1–2 MDa) protein assemblies consisting of multiple widely conserved and highly interconnected subunits, including a central Snf2 family ATPase (**Figure 1*a***). Recent advances illuminate the structure and composition of these complexes in animals and plants.



ySWI/SNF	yRSC	pBAF	cBAF	ncBAF
SNF2	STH1	BRG1	BRG1	BRG1
ARP7, ARP9	ARP7, ARP9	ARP4, ACT	ARP4, ACT	ARP4, ACT
SWI3	RSC8	SMARCC1, SMARCC2	SMARCC1, SMARCC2	SMARCC1
SNF12	RSC6	SMARCD1, SMARCD2, SMARCD3	SMARCD1, SMARCD2, SMARCD3	SMARCD1
SNF5	SFH1	SMARCB1	SMARCB1	—
SNF6	HTL1	SMARCE1	SMARCE1	—
SWI1	RSC9	ARID2	ARID1A, ARID1B	—
SWP82	RSC7	PHF10	DPF1, DPF2, DPF3	—
—	RSC58	BRD7	—	BRD9
—	RSC2, RSC4	PBRM1	—	—
RTT102	RTT102	—	—	—
—	RSC3, RSC30	—	—	—





(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

Subunit composition and structure of the SWI/SNF family CRCs. (*a*, *above*) Overview of four different SWI/SNF CRCs bound to nucleosomes [PDB ID entries: 6UXW (ySWI/SNF), 6KW3 (yRSC), 6LTJ (cBAF), 7VDV (pBAF)]. Note that some parts of the individual polypeptide chains are not displayed as they were not resolved in the original structures listed above. (*Below*) Legend indicating proposed homologies between the subunits of different complexes. Nucleosomal histones are colored gray and DNA is colored white. pBAF is used as an example to illustrate the position of structural features discussed in the text. (*b*) Hypothetical composition of the ncBAF and cBAF architectures in plants. Complex-specific subunits are outlined with a double line. White circles indicate subunits absent from panel *a*. The question mark signifies the unknown composition of the SYD-based complex. (*c*) Multiple sequence alignment of the *Arabidopsis*, yeast, and human SWI/SNF ATPases. The histogram indicates overall conservation, and the grayscale shading indicates similarity to the consensus sequence. Protein domains are labeled above the alignment. Purple bars below the alignment mark BRG1 fragments resolved in the pBAF structure (PDB ID: 7VDV). The ~ symbol indicates that the polypeptide chain continues beyond the alignment. Fuzzy color-coded bars below the zoomed-in view mark the estimated proximity of the base module subunits to different fragments of the ATPase subunit. (*d*) A zoomed-in view of the pBAF structure showing the path of the BRG1 polypeptide (*purple*) through the base module. The QLQ and HSA labels indicate positions of the BRG1 domains covered by the alignment in panel *c*. Note a gap in the BRG1 structure indicated by the dashed straight fragment of the image at the top left. ChimeraX 1.4 (**https://www.cgl.ucsf.edu/chimerax/**) was used for molecular graphics and Geneious Prime 2022.1.1 (**https://www.geneious.com/**) was used for multiple sequence alignment and display. Abbreviations: BD, bromodomain; CRC, chromatin remodeling complex; DBL, DNA binding lobe; HBL, histone binding lobe; NBL, nucleosome binding lobe; PDB, Protein Data Bank.

High-resolution cryo-electron microscopy (cryo-EM) structures of two yeast SWI/SNF CRCs, yRSC (86, 121, 138) and ySWI/SNF (40), and of two mammalian SWI/SNF CRCs, cBAF (42) and pBAF (143), show many common features. SWI/SNF CRCs contact core histones on both sides of the nucleosome and the nucleosomal DNA near superhelical position 2 (**Figure 1*a***). Each of the four complexes can be subdivided into three clearly defined modules: (*a*) the motor module formed by the helicase and SnAC domains of the ATPase subunit; (*b*) the actin-related protein (ARP) module, consisting of the α-helical HSA domain of the ATPase subunit bound by the ARP7-ARP9-RTT102 trimer (SWI/SNF, RSC) or the BAF53A-β-actin dimer (cBAF, pBAF); and (*c*) the base module, comprising the remaining subunits attached to the N-terminal preHSA domain of the ATPase subunit directly or through other subunits (**Figure 1*a***).

Each of the three modules plays a distinct role. The motor module hydrolyzes ATP to translocate along DNA and locally disrupts the DNA-histone contacts (20). The ARP module connects the motor with the base module and enhances coupling of ATP hydrolysis to DNA translocation, thus promoting remodeling and controlling its outcome (nucleosome sliding or eviction) (5). The base module, also known as the substrate recruitment module (138), provides a multivalent interface with the nucleosomal substrate that is critical for efficient remodeling and proper regulation by the local chromatin context (76). The base module subunits form three lobes that bind to (*a*) the nucleosome surface opposite to that bound by the SnAC domain (nucleosome binding lobe), (*b*) histone tails (histone binding lobe), and (*c*) the DNA through non-sequence-specific contacts (DNA binding lobe) (138) (**Figure 1*a***). These interactions depend on histone posttranslational modifications and DNA sequence features, therefore linking the outcome of the remodeling reaction to the genomic and the chromatin context.

Actin-related proteins (ARPs): a small, conserved family of actin relatives often found as monomers or heterodimers within chromatin remodeling complexes

Enhancer: DNA region bound by multiple transcription factors that link to promoters to upregulate transcription

In animals, three distinct SWI/SNF CRC subtypes exist: canonical (cBAF), polybromo (pBAF), and noncanonical (ncBAF) (78). In vivo, the three BAF complexes display distinct patterns of genomic distribution indicative of different activities. cBAF and pBAF bind to enhancers and promoters, respectively, and promote DNA accessibility for transcriptional regulation. ncBAF binds to promoters and to genomic regions bound by the architectural protein CTCF, suggesting a dual role in promoter accessibility and chromatin looping (78). All three CRC subtypes share a common ARP module and three common base module subunits: SMARCC, SMARCD (**Figure 1*a***), and BCL7 (78). A trimeric complex between a SMARCC dimer and one copy of SMARCD serves as a nucleation center during the sequential assembly of all mammalian BAF complexes (77).

Another two base module subunits, SMARCB and SMARCE, are shared only between cBAF and pBAF (**Figure 1*a***). These two subunits are crucial for nucleosome binding and complex stability, respectively (108, 116). cBAF and pBAF are distinguished primarily by alternative paralogous subunits: ARID1A/ARID1B and DPF1/DPF2/DPF3 (cBAF) or ARID2 and PHF10 (pBAF) (79) (**Figure 1*a***). Other subunits are unique to one specific BAF subtype (multi-bromodomain subunit PBRM1 and BRD7 of the pBAF histone binding lobe module, equivalent to the yRSC double-bromodomain subunits RSC1/RSC2 and RSC4, and the single-bromodomain subunit RSC58, respectively) (143) (**Figure 1*a***). The recently characterized ncBAF deviates from the canonical architecture shared by cBAF and pBAF by lacking core subunits SMARCB, SMARCE, and ARID and instead contains GLTSCR1 or its paralog GLTSCR1L (1, 78) (**Figure 1*a***). ncBAF and cBAF share the SS18 subunit, while both ncBAF and pBAF contain a BRD family subunit, BRD9 and BRD7, respectively (78, 79) (**Figure 1*a***).

Bromodomain: a protein reader domain that can bind acetylated lysines on histone tails, found in chromatin remodelers or histone posttranslational modifiers

Compositional diversity of the three mammalian BAF subtypes also translates to their substrate specificity. Nucleosome binding and remodeling activity of cBAF, pBAF, and ncBAF are differentially affected by histone modifications of the substrate nucleosome in vitro (76). Polyacetylation of H4 inhibits cBAF and pBAF but stimulates ncBAF, while another active chromatin mark, H3K4me3, specifically inhibits cBAF, especially when combined with H4 acetylation (76). Stable chromatin association and remodeling activity of all three complexes are promoted by polyacetylation of H3 or by H3K14ac alone (76). Surprisingly, H3K27ac and H3K4me1, two chromatin marks that colocalize with cBAF at active enhancers, inhibit its enzymatic activity in vitro (76).

Some BAF subunits are encoded by small gene families with preference for specific BAF complex subtypes (78) (**Figure 1*a***). In addition, unique, cell-type-specific, BAF complex subunits are required for cell lineage entry, choice, and progression. To switch from embryonic stem cells to neuronal progenitors, SMARCD2 is lost, while BRAHMA (BRM) and SMARCC2 contribute in addition to BRG1 and SMARCC1 (44). Transition from neural progenitor cells to neurons involves incorporation of SMARCD3 in addition to SMARCD1, replacement of PHF10 and DPF2 by DPF1 and DPF3, replacement of ARP4A by ARP4B, and replacement of SS18 by CREST. Cardiac development depends on SMARCD3 and on BRM (46). Altered complex composition is facilitated by tightly regulated changes at the level of expression of paralogous subunits (44) that likely affect all three BAF subtypes described above. These changes in complex composition may alter BAF targeting during development.

cBAF and pBAF are equivalent to ySWI/SNF and yRSC, while the ncBAF architecture is absent in yeast but conserved in other fungi (43). Phylogenetic analyses suggest that the cBAF-ncBAF divergence dates back to the last eukaryotic common ancestor, whereas the cBAF/ySWI/SNF and pBAF/yRSC subtypes appear after the split between plants and fungi/mammals (43). Homologs of both the common and the BAF-subtype-specific subunits are found throughout the eukaryotic domain of life (43); therefore, we use the framework of cBAF, pBAF, and ncBAF to discuss plant SWI/SNF complexes.

2.2. SWI/SNF Complexes in Plants Form Around Three Different Classes of Snf2 ATPases

Almost all subunits of the SWI/SNF family CRCs have orthologs in plants. Three *Arabidopsis thaliana* ATPases, BRM, SPLAYED (SYD), and MINUSCULE1 (MINU1)/MINU2 (motor module); two ARPs, ARP4 and ARP7 (ARP module); and base module subunits SWI3A/SWI3B/SWI3C/SWI3D, SWP73A/SWP73B, BSH, and ANGUSTIFOLIA3 (AN3) are well-established SWI/SNF family CRC components (reviewed in 98). Recent characterization of the cBAF subunit

homologs Leaf- and Flower-Related (LFR) (homolog of SWI1, RSC9, ARID1A/ARID1B, and ARID2) and TPF1/TPF2 (DPF1/DPF2/DPF3, PHF10 homolog), and of the ncBAF subunit homologs BRAHMA-interacting proteins 1 and 2 (BRIP1/BRIP2; GLTSCR1/GLTSCR1L homolog) and BRD1/BRD2/BRD13 (homolog of RSC58, BRD7 and BRD9), indicates that the cBAF-ncBAF dichotomy applies to the SWI/SNF CRCs in plants (43, 51, 71, 141, 142) (**Figure 1*b***). Surprisingly, it seems increasingly likely that MINU1 and MINU2 are subunits of plant cBAF-like CRCs and BRM is a component of a plant ncBAF-like CRC. This is in contrast to mammals, in which ATPases BRG1 and BRM are interchangeable between different BAF subtypes (1, 43). Of note, the plant Snf2 ATPases BRM, MINU, and SYD differ substantially in their domain architecture: Only BRM has a bromodomain, SYD has a long autoinhibitory C-terminal domain that is cleaved off at the onset of reproductive development, and the MINUs have very short N-terminal and C-terminal domains (55, 111) (**Figure 1*c***).

2.2.1. Noncanonical SWI/SNF complexes in plants. The *Arabidopsis* homologs of the ncBAF-specific subunit GLTSCR1/GLTSCR1L, BRIP1 and BRIP2, associated physically and genetically with BRM (142) and copurified with *Arabidopsis* SWI/SNF subunits AN3, SWI3C, and SWP73B (118) and with maize AN3 (81). In addition, BRD1, RBD2, and BRD13, homologs of the ncBAF-specific subunit BRD9, copurified with BRM, SWI3C, SWP73B, ARP4, and AN3 in *Arabidopsis* and with AN3 in maize (8, 51, 81, 118, 141). Loci bound by BRIP1/BRIP2 and BRD1/BRD2/BRD13 show a high degree of overlap with targets of BRM, whose chromatin association is much reduced in the *brip1 brip2* double and *brd1 brd2 brd13* triple mutants (141, 142). This overlap strongly suggests BRM forms an ncBAF complex in *Arabidopsis* (**Figure 1*b***).

The 3D structure of ncBAF has not yet been resolved; however, the recently published cryo-EM structure of pBAF shows a tight connection between the BRD9 paralog BRD7 and base module subunits shared by ncBAF and pBAF (143). The plant ncBAF-like complex may recruit a single-BRD subunit through multiple direct contacts with SWI3, SWP73, and the N-terminal part of the ATPase subunit (**Figure 1*c*,*d***). Direct interactions of BRD1/BRD2/BRD13 with BRIPs are also likely, if the location of BRIPs in the hypothetical *Arabidopsis* ncBAF-like complexes is equivalent to the location of ARID2 in pBAF (143) (**Figure 1*c*,*d***). Such BRD–base module interactions were recently confirmed by two independent studies but may point to co-recruitment of more than one BRD subunit to the same complex, especially since BRD1, BRD2, and BRD13 interact with each other (51, 141). A multi-BRD ncBAF in embryonic stem cells was recently described (34).

Affinity purification followed by mass spectroscopy (AP-MS) data suggest exclusive association of *Arabidopsis* ncBAF subunits BRIP1/BRIP2 and BRD1/BRD2/BRD13 with BRM (43, 51, 141, 142). The apparent epistasis of *brm-1* null mutants with *brip brip* double or *brd brd brd* triple mutants suggests that these proteins have little role outside of the complex with BRM (141, 142). Moreover, BRM does not pull down homologs of cBAF subunits LFR, BSH, or TPF1 when used as bait in AP-MS (141). However, genetic evidence suggests that BRM has functions outside of the ncBAF-like complex formed with BRIPs and BRDs, since the phenotype of the strong *brm-1* mutant is more severe than the phenotypes of the *brip1 brip2* double or the *brd1 brd2 brd13* triple mutants (51, 141, 142). In addition, BSH tethering resulted in SWI/SNF activity that depends on BRM presence, suggesting that BRM may also form a functional complex with cBAF subunits (131).

2.2.2. The canonical plant SWI/SNF complexes include MINU1/MINU2. In the course of evolution, the ancestral cBAF complex gave rise to several specialized complexes: cBAF and pBAF in mammals and ySWI/SNF and yRSC in budding yeast. In yeast and mammals, the ARM repeat domains of SWI1 and ARID1A/ARID1B are located at the center of the canonical-type

base module (40, 42, 138, 143) (**Figure 1*a***). They serve as a rigid platform for interactions between other subunits and, together with the SANT domains of SWI3 homologs, anchor the ATPase subunit to the base module (42, 77, 124, 138). LFR, an ARM repeat protein described in *Arabidopsis* (127) and rice (90), shares a common origin with SWI1 (ySWI/SNF), RSC9 (yRSC), ARID1A/ARID1B (cBAF), and ARID2 (pBAF) (43). Physical association between LFR and plant SWI/SNF subunits was detected by AP-MS (8, 43, 81, 118) and confirmed by multiple independent targeted protein interaction assays, providing support for conservation of this subunit in plants (43, 71). Recent AP-MS data show reciprocal copurification of TPF1/TPF2 with MINU2 and multiple shared interactions with canonical architecture subunits as well as several other proteins awaiting characterization (26) (**Figure 1*b***). *Arabidopsis* cBAF-like complexes most likely specifically incorporate MINU1 and MINU2.

PHD domain: a protein reader domain that can bind methylated lysines on histone tails

In agreement with their crucial structural function, loss of ARM repeat homologs of LFR impairs viability in budding yeast (22) and *Drosophila* (91) and is embryo lethal in mouse (33). Homozygous *lfr* mutants are embryo lethal in rice but viable in *Arabidopsis* (90, 127), which is surprising given the embryo lethality of double null mutant combinations of *Arabidopsis* ATPases MINU1 and MINU2 (7, 97). One possible explanation is that an unrelated protein substitutes for LFR in the canonical *Arabidopsis* SWI/SNF complexes.

The tandem PHD domains of the cBAF-specific subunit DPF1/DPF2/DPF3 bind to acetylated N-terminal tails of histones H3 and H4 (48, 145). Two different PHD domain proteins were recently identified as potential subunits of the plant cBAF-like complex. The triple-PHD domain protein TPF1 is physically associated with cBAF-specific subunits LFR and BSH, but not with ncBAF-specific BRIP1/BRIP2 and BRD1/BRD2/BRD13, underscoring conservation of the canonical architecture in plants (43). In addition, the single-PHD domain protein ONE PHD FINGER 1 (OPF1) was also identified as a potential TPF1 interactor by immunoprecipitation followed by MS. TPF1 and OPF1 each have a paralog in *Arabidopsis*, which may explain why their association with plant BAF complexes evaded detection through forward genetic screens. If the PHD domains of TPF1/TPF2 and OPF1/OPF2 are specific H3ac readers, then MINU cBAF-like complex activity could be modulated through multivalent interactions with acetylated histone tails, reminiscent of the animal pBAF or yeast RSC complexes.

No data are available to help classify SYD as a canonical or noncanonical BAF complex subunit. BRM and SYD co-occupy 50–70% of genic targets (105), and mutants lacking either BRM or SYD show shared and unique phenotypes and gene expression defects (7, 130, 131). Thus, whether SYD is part of an ncBAF-like or of a cBAF-like complex, BRM and SYD act jointly at many target loci (130, 131).

After acceptance of this review, comprehensive AP-MS analysis in *Arabidopsis* and rice confirmed three types of complexes organized around BRM, SYD, and MINU1/MINU2 (150). The study determined the subunit composition of the SYD-containing complex and proposed it to be equivalent to cBAF, based on preferential localization to the intergenic regions and distal promoters. In addition, the subunit composition and proximal promoter preference suggest a possible functional analogy between the MINU-containing complex and pBAF. pBAF and cBAF in animals evolved after the split between plants and animals (42); whether both subtypes exist in plants awaits future research.

3. ACTIVITIES OF SWI/SNF COMPLEXES IN THE NUCLEUS

3.1. Transcription

SWI/SNF remodelers activate or repress transcription in the context of chromatin in yeast, animals, and plants and act at multiple steps, including enhancer activity, recruitment of the

Pioneer transcription factors (pioneer TFs): class of transcription factors able to bind their cognate binding sites in condensed chromatin

Core promoter: region located upstream of the transcription start site to which RNA polymerase is recruited

Nucleosome-depleted region: often found at promoters and flanked by two well-positioned nucleosomes, the −1 nucleosome upstream and the +1 nucleosome downstream

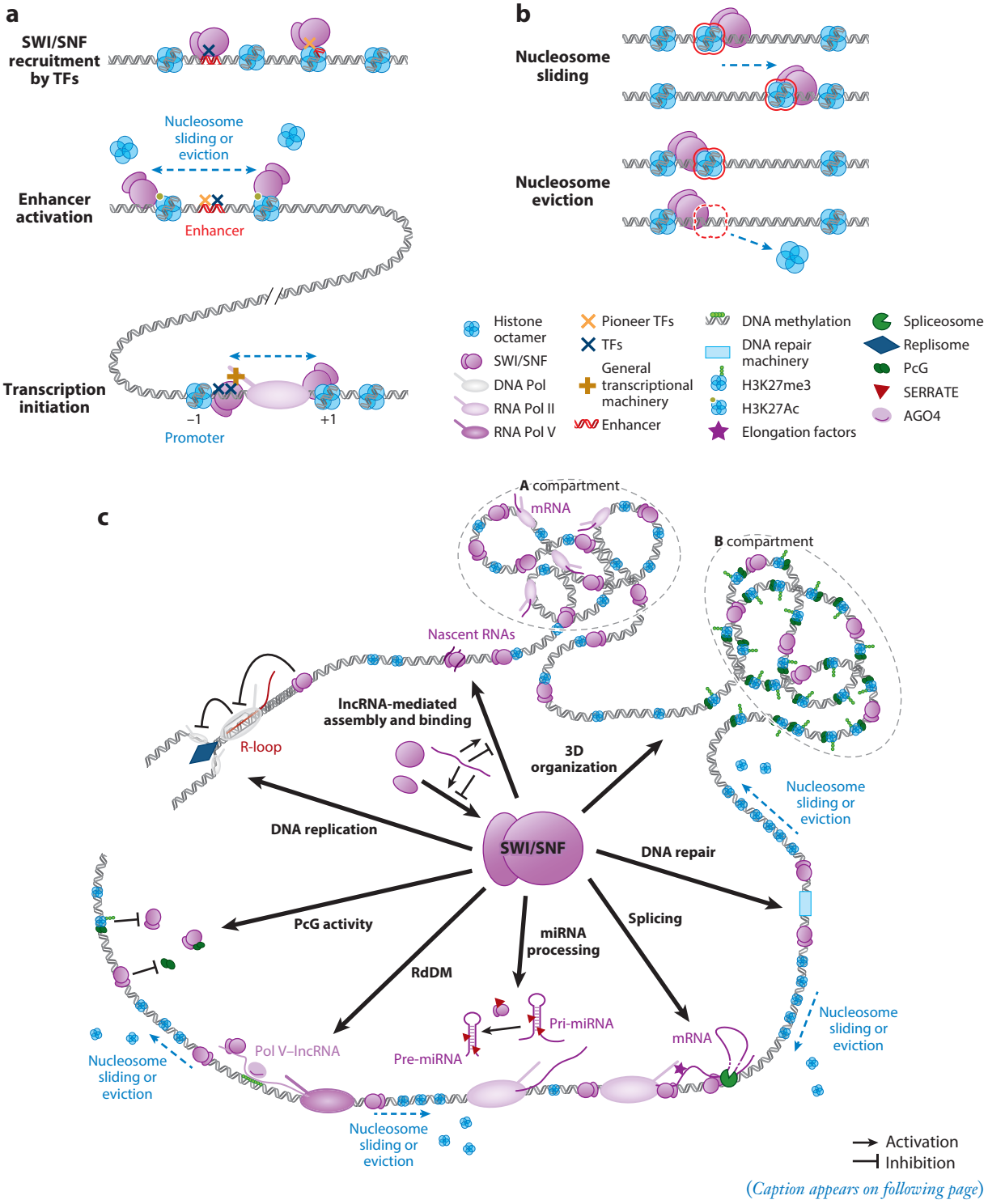
general transcriptional machinery to the promoter, and the switch from paused to elongating RNA polymerase (**Figure 2*a***). The relationship between chromatin remodelers and enhancer-binding transcription factors (TFs) is complex. On the one hand, CRCs, including SWI/SNF, cannot recognize specific DNA sequences on their own and are recruited to the genomic DNA by TFs. On the other hand, the SWI/SNF CRCs are required to enhance accessibility of TF-binding sites at enhancers. Hence, most TFs recruit SWI/SNF via *cis*-motifs located in the nucleosome free linker DNA between adjacent nucleosomes (144). In addition, a special class of TFs, termed pioneer TFs, can uniquely access their cognate *cis*-motifs in the context of the nucleosome in both animals and plants (58, 67, 144) (**Figure 2*a***). Pioneer TFs are thus well suited to initiate cell fate reprogramming in closed chromatin (144). TF-mediated SWI/SNF chromatin remodeler recruitment in turn reduces nucleosome occupancy or moves nucleosomes away from *cis*-motifs on enhancers; this enables binding of additional TFs required for full transcriptional output (**Figure 2*b***). In mammals, SWI/SNF also cooperates with the histone acetyltransferase p300 that acetylates H3K27 at enhancers (144).

Until recently, it was thought that once TFs have recruited SWI/SNF CRCs to enhancers, the enhancers remained open/accessible and engaged with TFs. Acute depletion of SWI/SNF instead revealed a need for continued presence of SWI/SNF CRCs. Depletion or inactivation of BRG1 and BRM in embryonic stem cells or a leukemia cell line reduced DNA accessibility at BRG1/BRM-bound distal enhancers within minutes, independent of the cell cycle (50, 101). The decrease in chromatin accessibility caused loss of TF binding and preceded transcriptional changes and loss of H3K27ac. These effects were most rapid at low-activity enhancers and occurred more slowly on highly open, H3K27ac-enriched, superenhancers bound by many TFs. Thus, continuous SWI/SNF activity is required for enhancer activity (50, 101). The reason for this is not clear; perhaps it ensures timely inactivation of enhancers no longer needed as cells progress along lineage trajectories. In animals, different SWI/SNF subtypes with alternative paralogous subunits aid in cell fate transition during differentiation (44, 45).

Similar loss of enhancer accessibility was observed upon depletion of the ARID1A subunit of the SWI/SNF CRC in mouse embryonic stem cells (9). When inhibition of SWI/SNF activity is reversed, the initial enhancer accessibility pattern rapidly reforms, indicating that reestablishment depends on cell-intrinsic properties. It will be interesting to determine how accessible sites, that are present prior to inhibitor treatment, are bookmarked for reestablishment of SWI/SNF occupancy; does histone acetylation or presence of histone variants contribute to enhancer bookmarking, or is the SWI/SNF CRC rerecruited by TFs? Regardless of the mechanism, these findings indicate that SWI/SNF CRCs are required for both initiation and maintenance of chromatin accessibility at enhancers.

In plants, no conditional depletion of BRM, SYD, or MINU1/MINU2 Snf2 ATPases and associated proteins has been reported, and SWI/SNF CRC components were reported to bind preferentially near the 5′ and 3′ region of genes in *Arabidopsis* (4, 26, 54, 69, 105, 142). Of note, many enhancers are close to the transcription start site (TSS) in the gene-dense *Arabidopsis* genome (93). BRM and SYD do occupy enhancers at key target loci, including *WUSCHEL* (*WUS*), *TARGET OF FT AND SOC1* (*TFS1*), *LEAFY* (*LFY*), *APETALA3* (*AP3*), and *AGAMOUS* (*AG*), and the *mir156a* locus (65, 94, 112, 130–132). It will be critical to examine whether SWI/SNF CRCs are also needed for maintenance of enhancer activity in plants.

A second role of SWI/SNF CRCs in transcription is to facilitate access of RNA polymerase II (Pol II) to the core promoter. Pol II is recruited to the nucleosome-depleted region between the −1 and +1 nucleosomes, which flank the core promoter (20). In yeast and mammals, different CRCs jointly modulate the spacing between the −1 and +1 nucleosomes and the positioning of the +1 nucleosome relative to the TSS (64). Degradation of yRSC and ySWI/SNF complexes



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Activity of SWI/SNF in the nucleus. (*a*, *top*) Pioneer TFs and SWI/SNF can access DNA in the context of the nucleosome, whereas nonpioneer TFs bind linker DNA to recruit SWI/SNF complexes. (*Middle*) Accessible enhancer after eviction and sliding of nucleosomes. (*Bottom*) At promoters, SWI/SNF enhances the distance between the −1 +1 nucleosomes, promoting binding of Pol II and of the general transcriptional machinery. (*b*) SWI/SNF CRCs alter chromatin accessibility by changing nucleosome positioning and occupancy. (*c*) Additional roles of SWI/SNF CRCs in nuclear processes and SWI/SNF interactions with RNA. Abbreviations: CRC, chromatin remodeling complex; lncRNA, long noncoding RNA; mRNA, messenger RNA; miRNA, microRNA; PcG, Polycomb group; Pol, polymerase; pre-miRNA, precursor miRNA; pri-miRNA, primary miRNA; RdDM, RNA-directed DNA methylation; TF, transcription factor.

in yeast indicated that both push the +1 nucleosome away from the TSS, enabling recruitment of Pol II and the general transcriptional machinery at most (yRSC) promoters or at TATA-box-containing (ySWI/SNF) promoters; this prevents the use of an alternative TSS (64). In *Arabidopsis*, the BRM CRC shifts the +1 nucleosome over the TSS of drought-responsive genes to prevent their transcription in the absence of stimulus (39). Subsequent to Pol II loading, the mammalian SWI/SNF CRC promotes accumulation of paused Pol II at promoters; depletion of ARID1A led to decreased transcription because of reduced accumulation of paused Pol II, not because of reduced transcription initiation or impaired elongation (114). In summary, SWI/SNF can trigger, maintain, and increase enhancer activity and open the core promoter for the transcriptional machinery. In other contexts, SWI/SNF CRCs block transcription, for example, by sliding nucleosomes to occlude *cis*-regulatory elements in enhancers or to prevent access to the TSS (see Section 4.2).

3.2. SWI/SNF CRCs Can Overcome Polycomb-Mediated Silencing of Gene Expression

Polycomb group (PcG) epigenetic regulators silence transcriptional programs that are not needed in or that are detrimental to a given cell type, developmental stage, or condition. PcG complexes PRC2 and PRC1 deposit repressive histone modifications, including H3K27me3. Genetic suppressors of homeotic defects in PcG mutants are collectively referred to as Trithorax group (TrxG) proteins; among this group of proteins are components of the SWI/SNF CRC in *Drosophila*, mammals, and plants (63, 130). In mammalian embryonic stem cells, tethering of BAF led to rapid eviction (within minutes) of both PRC1 and PRC2 and increased chromatin accessibility in an RNA Pol II–independent manner, likely due to direct interactions between BAF components BRG1 or SMARCC1 and PRC1 (62, 109). In vitro, the addition of PRC1 to nucleosomes, prior to the addition of SWI/SNF, blocks SWI/SNF chromatin remodeling activity (103). Moreover, rapid BAF depletion in vivo causes redistribution of PRC1 and PRC2 from highly repressed Polycomb-occupied loci, such as the *HOX* genes, to weakly occupied sites, where PcG binding is opposed by BAF (128). Conversely, depletion of PRC1 did not affect BAF occupancy. At some PcG target loci, BRG1 also directly aids in repression, perhaps in concert with regulators such as histone deacetylases (128) (**Figure 2*c***). Hence, SWI/SNF CRCs can eject PcG complexes and block PcG access to chromatin at many loci.

PRC1 and PRC2: multisubunit protein complexes that monoubiquitylate H2AK119 (H2AK121 in plants) or methylate H3K27 for chromatin condensation and stable gene silencing

Trithorax group (TrxG) proteins: chromatin-associated proteins promoting gene expression by opposing the repressive activities of the Polycomb group (PcG) proteins

Likewise in *Arabidopsis*, antagonistic roles of SWI/SNF and PRC2 at many developmental gene loci were reported. One example is reversal of Polycomb repression at the floral homeotic genes *AP3* and *AG* that direct flower patterning by BRM and SYD (130). Indeed, loss of *syd* or *brm* can overcome homeotic defects of mutants in PRC2, in agreement with the classic definition of PRC2 and TrxG activity (130). Furthermore, the *TFS1* gene is antagonistically regulated by PcG and by a H3K27me3 histone demethylase together with BRM to modulate flowering time in *Arabidopsis* (94). Likewise, at the *mir156a* locus, which prevents the transition from juvenile to adult traits, opposite roles were described for BRM and H3K27me3 (132). Moreover, increased

H3K27me3 was observed at a small subset of loci in constitutive *brm* or *syd* mutants, including the MADS-box floral repressor *SVP* and the homeodomain ovule identity gene *BEL1* (68). BRM colocalizes with the H3K27me3 demethylase REF6 at a subset of target loci in *Arabidopsis* and it has been proposed that REF6 recruits BRM (69). On the other hand, a recent study reported a decrease of H3K27me3 in domains that become active in *brm* mutants (134), reminiscent of the redistribution of H3K27me3 observed upon BAF depletion in mammals (128). Hence, in both animals and plants PcG and SWI/SNF coordinately shape the accessible chromatin landscape during development. This finding is remarkable, as the last common ancestor between these two kingdoms was unicellular.

3.3. Role of SWI/SNF in Loop Formation for Transcription

DNA packaged within the nucleus forms loops of varying sizes that can impinge on gene expression in yeast, animals, and plants (6, 72). Large-scale chromatin loops seen in mammals form so-called topologically associated domains (TADs) that limit enhancer–promoter contacts to those present inside the same compartment (6). TAD boundaries are enriched in architectural proteins such as CTCF. BRG1/ncBAF also associates with TAD boundaries and *BRG1* knockdown reduced TAD integrity (6) (**Figure 2*c***). In addition, tandem mass spectrometry identified BRG1 as a direct partner of CTCF (75). The *Arabidopsis* genome is not composed of TADs but like mammals has active (A) and repressed (B) chromatin compartments and locus-specific chromatin looping that involves contacts between 5′- and 3′-ends of gene bodies that boost enhancer–promoter interactions (72). The SWI/SNF CRC–containing SWP73B prevents the formation of an activating loop both at the *FLC* locus, an important repressor of flowering (53), and at two cytokinin biosynthesis genes (*IPT3* and *IPT7*) in the root (52). Recent chromatin conformation studies of *Arabidopsis* revealed that chromatin remodeler mutants, including *brm*, have fewer of these chromatin loops (137). The authors also identified shifts from repressed (B) to active (A) chromatin compartments, consistent with globally reduced H3K27me3 as well as increased H3K37me3 at specific loci, as discussed above (137) (**Figure 2*c***). As larger plant genomes form chromatin compartments that more closely resemble TADS, it will be interesting to determine the role of SWI/SNF in genome compartmentalization in these species.

3.4. SWI/SNF Contributions to Gene Expression Beyond Transcription

Here, we discuss the role of SWI/SNF complexes in gene expression beyond transcription. SWI/SNF contributes to gene expression by promoting de novo DNA methylation and regulating microRNA (miRNA) processing and influences splicing in both plants and mammals. Additionally, we will highlight the role of SWI/SNF in other nuclear processes, such as DNA repair and replication.

3.4.1. DNA methylation. In *Arabidopsis*, SWI3B promotes de novo DNA methylation at transposable elements by associating with the INVOLVED IN DE NOVO 2 (IDN2) and IDN2 PARALOGUE (IDP) complex that binds to Pol V–dependent long noncoding RNAs. SWI/SNF alters nucleosome positioning near Pol V transcription sites to promote RNA-directed DNA methylation (147) (**Figure 2*c***). In parallel, the SWI/SNF component SWI3B physically interacts with histone deacetylase HDA6 in *Arabidopsis* to repress transcription of a subset of transposons (135).

3.4.2. microRNA processing. In *Arabidopsis*, BRM promotes transcription of miRNA genes but blocks the accumulation of mature miRNA. Together with the zinc finger protein SERRATE,

Chromatin loop: structure formed through close proximity of distant DNA regions in TADs or enhancer–promoter interaction

Topologically associated domains (TADs): self-interacting genomic regions that are relatively insulated from neighboring regions

Chromatin compartment: chromatin segregates into compartments A or B, characterized by different epigenetic features and active and repressed transcription, respectively

Long noncoding RNA: transcript of more than 200 nt in length, with a low coding ability and a function in its RNA state

RNA-directed DNA methylation: a mechanism by which small interfering RNAs and chromatin-related proteins guide de novo DNA methylation

R-loops: RNA:DNA hybrid formed when a single-stranded RNA molecule hybridizes with one of the DNA strands

a component of the microprocessor, BRM remodels primary miRNA secondary structures to inhibit miRNA maturation (**Figure 2*c***). In agreement, *BRM* inactivation results in a significant increase in mature miRNA accumulation (126). This role of BRM represents a large contribution to gene expression, in addition to the more canonical role in transcription. Moreover, the SWI/SNF CRC subunits SWI3B, SWI3D, and BSH interact with ARGONAUTE1 (AGO1), a protein linked to miRNA processing; however, this interaction activates gene expression at the transcriptional level (73). Likewise in human, BAF interacts with AGO2; the latter stabilizes the +1 nucleosome at certain loci (15).

3.4.3. Splicing. In both plants and mammals, nucleosomes accumulate in exons and may contribute to exon definition. In fission yeast, budding yeast, and *Drosophila*, SWI/SNF contributes to cotranscriptional assembly and recruitment of the spliceosome and promotes expression and splicing of intron-containing genes (**Figure 2*c***) by interacting with general splicing factors (32, 117, 122). In mammals, BRG1 and BRM promote splicing of some genes, such as *telomerase reverse transcriptase* (*TERT*) (49), but can also reduce the affinity between RNA binding factors linked to splicing and the RNA (32). Of note, recruitment of RNA binding factor to nascent RNAs for alternative splicing is independent of ATPase activity (32). Human and *Drosophila* BRG1/BRM also mediate alternative splicing by association with members of the cleavage and polyadenylation factor complexes (139). Environmental stimuli influence splicing in human, *Drosophila*, and fission yeast through SWI/SNF interaction with the small nuclear ribonucleoproteins U1 and U5 (56). In addition, the BAF CRC component SMARCE1 contributes to alternative splicing of *cyclin D1* in response to mechanical stress (31). Likewise in maize, the SWI3D ortholog ZmCHB101 contributes to alternative splicing under osmotic stress (140). The combined findings suggest that the multiple different contributions of SWI/SNF CRCs to gene expression are conserved across the kingdoms of life.

3.5. Other Roles in the Nucleus: SWI/SNF-Mediated DNA Repair and DNA Replication

SWI/SNF CRC subunits are mutated in nearly 25% of human cancers, and this role has been linked to many of its diverse nuclear functions, including gene expression and DNA repair and replication (61). In yeast and mammals, SWI/SNF CRCs facilitate DNA repair by enabling recruitment of DNA repair machinery through nucleosome eviction (92) (**Figure 2*c***). Indeed, decreased expression of *BRG1* and *BRM* in human cells reduced the efficiency of homologous recombination repair by 40–50% and 15%, respectively (41). Similarly in plants, RNA interference–mediated inhibition of the SWI/SNF subunit *SWI3B* enhanced DNA damage accumulation (57). SWI3B participates in the recruitment of structural maintenance complex 5 (SMC5), a chromosomal ATPase involved in double-strand break DNA repair (57). *Arabidopsis* BRM contributes to the DNA damage response possibly by promoting homologous recombination (102). In maize and *Arabidopsis*, CHC101/SWBP73B is upregulated by UV-B exposure; in maize, this prevented UV-B-induced DNA damage (14, 17).

Recently, transcription has emerged as a major source of genome instability during replication through the formation of transcription-dependent R-loops, DNA-RNA duplexes that collide with the replisome and result in accumulation of DNA breaks (21, 115). CRCs, including mammalian BAF, interact with R-loops and reduce their formation in cell lines (21, 115), thus lowering transcription–replication conflict and promoting replisome processivity along the DNA (**Figure 2*c***).

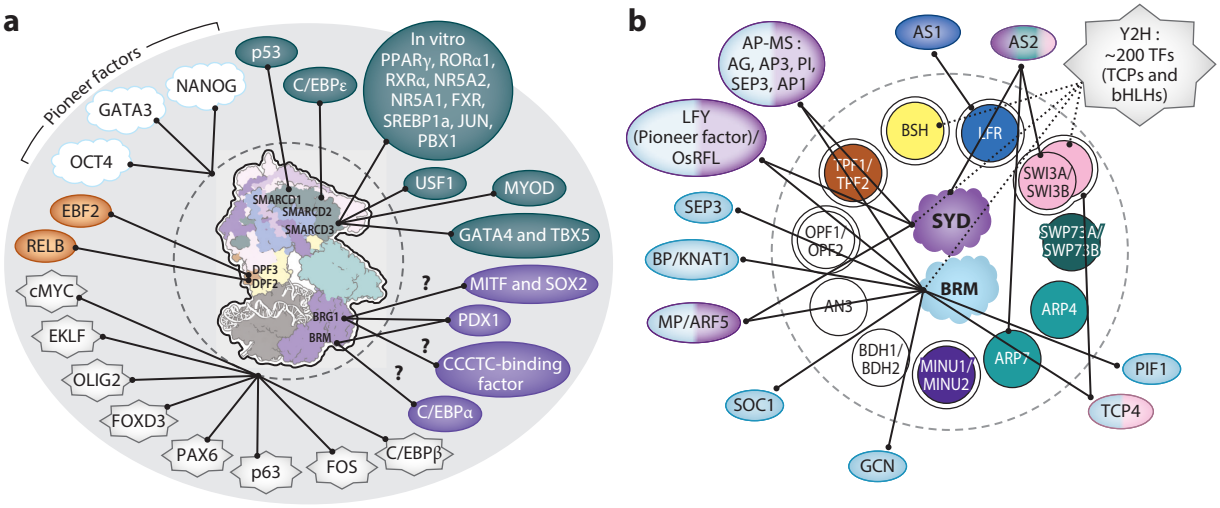


Figure 3

SWI/SNF recruitment to target loci by TFs in animals and plants. (*a*) Mammalian or (*b*) plant TF interactions with SWI/SNF CRC components. TFs are color-coded to indicate the SWI/SNF CRC subunit they contact. A Y2H screen (*gray star*) identified hundreds of SWI/SNF-interacting TFs in *Arabidopsis*. Since most of these interactions were not validated in planta, they are represented with dotted lines. Abbreviations: AP-MS, affinity purification followed by mass spectroscopy; CRC, chromatin remodeling complex; TF, transcription factor; Y2H, yeast two-hybrid.

4. BIOLOGICAL ROLES AND RECRUITMENT OF SWI/SNF CRCs

4.1. Development

The role and recruitment of SWI/SNF complexes in mammalian development have been reviewed (44, 45). BAF CRCs promote both pluripotency in embryonic stem cells and differentiation into diverse cell types, tissues, and organs (44, 45). Many TFs, including pioneer TFs OCT4, NANOG, and GATA3 in mammals and GAF in *Drosophila*, recruit SWI/SNF complexes to genomic target sites (38, 45, 60) (**Figure 3*a***). In addition, specific noncoding RNAs block or promote BRG1 occupancy at genomic loci (87) (**Figure 2*c***). Indeed, Pol II inhibition and RNase treatment cause widespread dissociation of BAF from the chromatin, implicating nascent RNA in stabilizing BAF chromatin association via its SMARCC1 subunit (106).

4.1.1. Role of SWI/SNF CRCs in pluripotency in plants. As in animals, SWI/SNF chromatin remodeling ATPases contribute both to maintenance of pluripotency and to the switch to differentiation. Unlike their animal counterparts, null *syd* and *brm* mutants have pleiotropic developmental defects but are viable, whereas loss of both ATPases causes gametophyte and embryo lethality (7). SYD maintains expression of the pluripotency gene *WUS* required for stem cell maintenance and meristematic activity of the shoot (65, 112). Another class of pluripotency genes is the class 1 *KNOX* genes, including *KNAT2*, *KNAT6*, and *BREVIPEDICELLUS* (*BP*). SYD downregulates *KNAT6* in differentiating leaves (111). The ASYMMETRIC LEAVES2 TF contributes to LFR occupancy at the *BP* locus to prevent leaf lobing; enhanced leaf defects are observed in *as2 lfr* double mutants (70). In the inflorescence, loss of BRM or of the dedicated BRM complex component SWI3C increases expression of *KNAT2* and *KNAT6* and results in reduced internode elongation and increased pedicel angles (149). BP directly recruits BRM to the *KNAT2* and *KNAT6* loci (149). Mutants in the recently duplicated genes *MINU1* and *MINU2*

have phenotypes reminiscent of replication-coupled chromatin assembly factors and cell cycle regulators (97). Weak/intermediate *minu1 minu2* double mutants arrest the shoot meristem and lose *WUS* expression; subsequently, one or multiple new meristems initiate and frequently fasciate (97). Single null mutants have no developmental defects, while the *minu1 minu2* double null mutant is embryo lethal (97). During leaf growth, the SS18 homologous subunit of plant SWI/SNF complexes AN3 (**Figure 1*b***), which copurifies with the SYD and BRM ATPases, toggles between cell division and expansion via interaction with different growth-regulating factor DNA-binding proteins in maize and *Arabidopsis* (81, 118).

4.1.2. SWI/SNF CRCs and differentiation in plant development. During differentiation, SYD and BRM are recruited to floral homeotic genes by the MADS-box TF SEPALLATA3 (SEP3) and by the pioneer TF LFY, and conditional *syd brm* double null mutants display strong floral homeotic defects (58, 130). The interaction between the LFY homolog RFL and the SWI/SNF ATPase SYD is conserved in rice (133). LFY interaction sites map to N-terminal domains of BRM and SYD, a 250-bp region that comprises the conserved HSA domain and the upstream HSA adjacent domain (amino acids 465–726 SYD and amino acids 638–855 BRM) (130). AP-MS of MADS-box TFs further supports SEP3 association with BRM and SYD CRCs and additionally implicates AP1, AP3, PISTILLATA, and AG in association with BRM and SYD CRCs (107). The identification two decades ago of two *syd* alleles as genetic enhancers of floral homeotic defects in weak *lfy* mutants in *Arabidopsis* was one of the first links between SWI/SNF CRCs and multicellular eukaryote development (120).

4.1.3 Onset of reproductive development. Plants can alter their form throughout their life cycle and go through distinct developmental stages controlled at the level of chromatin by the BRM SWI/SNF complex (reviewed in 113). BRM is important for the transition from seed to vegetative development, and for the juvenile to adult vegetative transition, and modulates flowering time. The effect of BRM on flowering time depends on endogenous and exogenous cues and is complex; *brm* mutants flower early in inductive photoperiod but late in noninductive conditions (30). Moreover, BRM represses expression of TFs that promote (*FT* and *SOC1*) and repress (*FLC*) flowering time and activates expression of two TFs with opposite roles in flowering time, *SVP* and *TSF1* (30, 68, 94, 113, 134). The GATA TF GCN recruits BRM to *SOC1* (134) and SOC1 recruits BRM to *TFS1* (94). In maize, a class IV HD-ZIP TF interacts with SWI3C1 to control flowering time (25).

4.2. Signaling Response: Intrinsic Cues

SWI/SNF remodelers act as the interface between chromatin and extrinsic or intrinsic cues (signaling) and alter chromatin and transcriptional programs in response to developmental and environmental cues to enhance plant growth and reproductive success (**Figure 4**). There is crosstalk between these processes: On the one hand, SWI/SNF CRCs have important roles in hormone accumulation and response; on the other hand, SWI/SNF recruitment and activity are dependent on hormonal cues. For example, chromatin remodeling and enhancer accessibility rely on SWI/SNF CRC recruitment by signaling TFs such as MONOPTEROS (MP) in response to auxin hormone sensing (110). Under low-hormone conditions, MP is prevented from contacting BRM or SYD SWI/SNF CRCs by the auxin-sensitive Aux/IAA proteins; this ensures that activation of genes that promote formation of new primordia occurs only at auxin maxima in inflorescences (131). Like LFY, MP binds to the N-terminal domain of SYD and BRM (131). Subsequent studies have identified additional links between the auxin pathway and the BRM SWI/SNF CRC, which directly promotes expression of the *PIN* auxin transport gene in the root meristem (136).

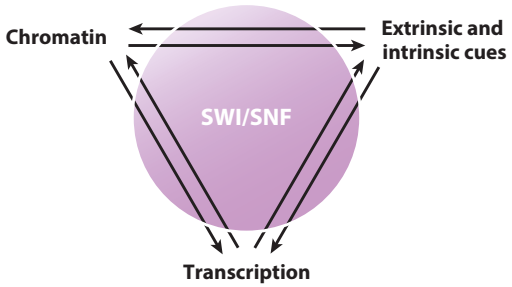


Figure 4

Chromatin remodelers are at the nexus of the interactions between signaling, TFs, and chromatin that together ensure proper organismal development and stress response. For example, SWI/SNF modulates chromatin to prevent stress responses in the absence of stress, with stress sensing in turn inactivating SWI/SNF. TFs recruit specific SWI/SNF CRC subtypes during development, and developmental fate progression requires SWI/SNF for selective enhancer activation and activity. Signaling can also gate TF–SWI/SNF interactions (auxin hormone levels control SWI/SNF interaction), while TFs tune signal production with the help of SWI/SNF CRCs. Abbreviations: CRC, chromatin remodeling complex; TF, transcription factor.

In addition, BRM and SWI3C promote gibberellin (GA) and inhibit cytokinin accumulation and response (2, 3, 29, 99, 100). *brm-1* and *swi3c* mutants have reduced levels of bioactive GA and directly activate the GA receptor *GID1*, the GA biosynthesis gene *GA3ox1*, and the GA response gene *SCL3* (2, 99). GA response is also misregulated in *syd* mutants (7). BRM and SWI3C promote expression of the cytokinin response inhibitor gene *ARR16* in leaves to trigger differentiation (29). The TEOSINTE BRANCHED, CYCLOIDEA, PCF4 (TCP4) TF recruits BRM to the *ARR16* locus, multiple *brm* alleles were identified in a genetic suppressor screen of *TCP4* gain-of-function mutants, and a large-scale, yeast two-hybrid TF interaction screen identified TCP4 as a direct interactor of BRM and SWI3C (29). In plants, many TF interactions with SWI/SNF have been mapped to the BRM or SYD ATPases, perhaps reflecting the defining role the ATPases have in forming unique SWI/SNF complex subtypes (**Figure 3*b***).

4.3. Signaling Response: Abiotic Signals (Extrinsic Cues)

Due their sessile nature, plants frequently mount stress responses in changing environments. One of the most conserved plant responses to abiotic stress is partial or complete growth arrest (104). Most SWI/SNF CRCs prevent this stress response in the absence of the stress stimulus, thus optimizing resource allocation to growth and development.

4.3.1. Response to drought and high salt. For example, *brm* mutants display derepression of the drought response genes and direct BRM targets *ABI5* and *ABI3*, trigger growth arrest prior to seedling establishment at low doses of the drought hormone abscisic acid (ABA), and display increased drought tolerance (39). Adult *Arabidopsis* plants treated with ABA or salt accumulate less BRM protein and have elevated *ABI5* expression (119). BRM in turn may modulate expression of the ABA signaling phosphatase PP2C in stress conditions. In response to salt stress, the *PP2C* locus switches from a repressed to an active state characterized by nucleosome eviction. This is likely mediated by BRM as *brm-3* loss-of-function mutants display higher upregulation of *PP2C* in response to salt stress (82). Inactivation of *SWI3C* enhances plant resistance to freezing and promotes expression of cold-responsive genes (*ICE1*, *CBF1*, and *MYB15*) via binding to their promoter in a temperature-dependent manner (36). Dwarfism and reduced root elongation of *brm*

and *swi3c* mutant plants decrease when ABA response is blocked and when plants are grown at lower temperature, respectively (39, 99). Opposite to *brm* mutants, *minu1* (*AtCHR12*) mutants display reduced growth arrest in response to drought, heat, and salinity stresses (80).

4.3.2. Heat and Light Stress. SWI/SNF-mediated changes of organism tolerance to elevated temperature in yeast have been reported, in which the inactivation of *SWP73* causes hypersensitivity to elevated temperature (13). In *Arabidopsis*, the heat-stress-induced histone deacetylase HD2C copurifies with SWI/SNF CRCs and attenuates heat stress response together with BRM (12). BRM also copurified with FORGETTER1 (FGT1) (11), an *Arabidopsis* ortholog of a metazoan developmental coactivator. *fgt1* mutants are defective in somatic heat stress memory. Inactivation of the BRM CRC reduced both heat stress tolerance and memory in plants (11). BRM and FGT1 co-occupy a subset of loci, and *fgt1* mutant plants showed altered nucleosome occupancy and positioning at shared target genes, such as *HSA32* (11). SWP73A and SWP73B also bind to many temperature- and light-responsive genes (53, 66, 118). For example, in response to high light and temperature, SWP73B accumulates in the nucleus and blocks the binding of PHYTOCHROME INTERACTING FAMILY (PIF) TFs to light-responsive genes; in the dark this is reversed as SWP73B levels drop (54). In addition, PIF1 interacts with and recruits BRM to light-responsive genes (146). Similarly, the expression of maize chromatin remodeler CHC101 (SWI3B-domain-containing protein) increases in response to UV-B, and CHC101 participates in plant acclimation to UV-B (16). Finally, decreasing SWI2/SNF2-like transcript abundance resulted in acute plant sensitivity to UV-B (17). An example of a role for BAF complexes in limiting stress responses to stress signal perception is mechanical stress in mammals. Low mechanical stress triggers an inhibitory interaction between ARID1A and two coactivators (YAP and TAZ) that prevents a stress response (19).

4.4. Signaling Response: Biotic Signals and Stress (Extrinsic Cues)

Both animal and plant SWI/SNF CRCs have been linked to pathogen response. Recently, the ncBAF subunit BRD9 was shown to inhibit glucocorticoid-mediated repression of inflammatory response in macrophages by blocking binding of the glucocorticoid receptor to a subset of its target sites (125). CRISPR screens uncovered a proviral role for SARS-CoV-2 for human BAF complexes, which may promote viral entry (129). Unlike animals, plants do not have an adaptive, antibody-based immune system and they do not have mobile cells to detect or fight an infection. Instead, plants rely on innate immunity, involving the combined action of phytohormones (salicylic acid, jasmonic acid, and ethylene) and stress-responsive genes, to defend themselves against pathogens (27). BRM-containing SWI/SNF participates in the transcriptional repression of pathogenesis-related genes in the absence of stress, as indicated by derepression of these genes in noninfected *brm101* mutant plants (7). Likewise, in the absence of stress, plant intracellular immune receptors, called nucleotide-binding leucine-rich repeat genes (NLRs), are directly silenced by SWP73A to avoid autoimmunity (47). Upon bacterial infection, plant small RNAs that silence *SWP73A* are upregulated, leading to immune response (47). In addition, the SYD CRC also represses the *NLR* gene *SUPPRESSOR OF NPR1, CONSTITUTIVE1* (*SNC1*) in the absence of biotic stress (59). SYD-containing SWI/SNF promotes the expression of jasmonate- and ethylene-responsive genes through binding to their promoter upon *Botrytis cinerea* infection (123). Loss of SYD activity resulted in increased sensitivity to *B. cinerea* but not to *Pseudomonas syringae*, highlighting the specificity of the SYD-mediated biotic stress tolerance (123). Moreover, *SYD* transcript abundance decreased upon treatment with ABA and salicylic acid but increased upon treatment with a bacterial peptide (flg22), indicating *SYD* may be regulated at the transcript level upon biotic stress (105). Thus, SWI/SNF CRCs frequently restrict abiotic and biotic

stress responses to stress conditions to prevent resource allocation to these pathways in nonstress conditions.

5. REGULATION OF SWI/SNF ACTIVITY

5.1. Posttranslational Modifications

Differential accumulation and incorporation of paralogous subunits are not the only mechanisms to regulate cell- or locus-specific chromatin remodeler activity. In addition, posttranslational modifications and altered conformation affect SWI/SNF complex activity. Posttranslational modifications also integrate environmental and developmental signals with SWI/SNF CRCs, affecting chromatin accessibility and transcription (**Figure 4**). Casein kinase 2 and extracellular signal-regulated kinases phosphorylate BRG1 during mitosis; the latter inactivates BRG1 and causes BRG1 dissociation from condensed chromatin. During DNA damage repair, the ATM kinase phosphorylates BRM to enhance association of its bromodomain with acetylated histones (H3K14ac) (84; reviewed in 45). SMARCD3 is phosphorylated by p38 during skeletal myogenesis, which together with MYOD enables chromatin targeting (85), and SMARCC2 phosphorylation enables neuronal differentiation (83). In plants, the BRM ATPase is constitutively bound to ABA-/drought-responsive loci to prevent their transcription in the absence of drought. Upon drought/ABA sensing, the SnRK2 kinase phosphorylates BRM at Ser1760 and Ser1762 to block BRM activity; this effect is reversed by PP2C phosphatases in the absence of the stimulus (39, 88). In addition, ubiquitin E3 ligases target BAF subunits for degradation to ensure proper complex stoichiometry in mammalian cells. In particular, the scaffold protein SMARCC1 is tightly regulated by ubiquitin-mediated degradation and stabilizes other core subunits to protect them from degradation (reviewed in 45). In *Arabidopsis*, BRM is targeted to the 26S proteasome for degradation in response to high boron levels to avoid DNA double-strand break in the root meristem (96). Likewise, *Arabidopsis* BRM is stabilized in roots via interaction with the SUMO E3 ligase MMS21 (148).

5.2. SWI/SNF Conformers and Prion-Like Domains

Protein conformers (protein isoforms that adopt different 3D conformations) connect genotype and environment and could possibly provide protein-based memory (24). Amyloid aggregate–forming prions harbor low-complexity protein regions, enriched in glutamine/asparagine (Q/N) residues, or short amyloid-prone sequences in their prion domains (PrDs) that can propagate prion conformers (95). Yeast Swi1, a subunit of the ySWI/SNF CRC, can form a prion state [*SWI*$^+$] and contains a PrD at its N terminus (amino acids 1–30), which is necessary and sufficient for self-perpetuation of the prion state (35). [*SWI*$^+$] also triggers aggregation of several TFs (28, 35). [*SWI*$^+$] shows enhanced sensitivity to environmental stress, characterized by partial loss-of-function and limited gain-of-function effects (28, 74). The role of the Q/N-rich canonical domain of the Swi1 orthologs in other organisms has not been explored. In addition, fusion proteins consisting of a prion-like domain (PLD) from one of the FET proteins (FUS, EWS1, or TAF15) and a TF DNA-binding domain can redirect BRG1 or other BAF CRC components to tumor-specific enhancers via PLD-PLD interactions to form condensates on DNA and globally rewire transcriptional programs (10, 23). In *Arabidopsis*, the PLAAC algorithm predicted hundreds of proteins with PLDs across the full proteome, including SWI/SNF CRC components BRM, SWI3C, AN3, and SWP73B (18, 89). In yeast, histidine residues in the N-terminal QLC (glutamine-rich low-complexity) domain of ySNF5 sense transient acidic pH during glucose starvation, which triggers a conformational expansion of the *SNF5* QLC to facilitate interaction with TFs that recruit ySWI/SNF to glucose-repressed loci (37). Thus, many different process-specific

SWI/SNF activities can be generated by changes in CRC composition, covalent modifications (posttranslational modifications) or protein conformation, or the chromatin context at target loci.

SUMMARY POINTS

Novel insight has been gained into SWI/SNF complex structures by cryo-electron microscopy and into the activity of these complexes by tethering them to chromatin or by triggering their depletion in animal cells. Across-kingdom comparisons have uncovered many similarities in composition, role, and regulation of SWI/SNF chromatin remodeling complexes (CRCs). Some of these recent findings are summarized below.

1. Two distinct architectures of the SWI/SNF complex (cBAF and ncBAF) are conserved in fungi, animals, and plants.
2. Whereas different SWI/SNF subtypes are defined by nonenzymatic subunits in animals, they likely form around distinct ATPases in plants.
3. SWI/SNF CRCs in animals are required to initiate and maintain enhancer accessibility.
4. SWI/SNF CRCs mainly oppose Polycomb repression but can indirectly or directly promote Polycomb silencing in eukaryotes.
5. RNA–SWI/SNF interactions underpin recruitment, transcription, DNA methylation, splicing, and microRNA maturation.
6. Eukaryote SWI/SNF complexes have conserved roles both in promotion of pluripotency and in differentiation.
7. SWI/SNF CRCs frequently prevent stress responses in the absence of the stress stimulus, perhaps to optimize resource allocation to growth and development.
8. SWI/SNF activities are stimulus gated via complex subunit abundance, posttranslational modifications, prion-like domains, and the local chromatin context.

FUTURE ISSUES

1. Do different plant CRC subtypes have unique nuclear roles or contribute differentially to gene expression via accessibility of core promoters, proximal enhancers, or distal enhancers?
2. Are there tissue-specific variants of the BRM, SYD, or MINU SWI/SNF CRCs in plants and what are their defining subunits?
3. What is the effect of acute SWI/SNF complex depletion on enhancer activity or on Polycomb repression in plants?
4. What is the role of nascent or long noncoding RNAs in SWI/SNF CRC recruitment or activity in plants?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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