MINIREVIEW

⌘ *Author's Choice*

SWI/SNF Chromatin-remodeling Factors: Multiscale Analyses and Diverse Functions*

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Chromatin-remodeling enzymes play essential roles in many biological processes, including gene expression, DNA replication and repair, and cell division. Although one such complex, SWI/SNF, has been extensively studied, new discoveries are still being made. Here, we review SWI/SNF biochemistry; highlight recent genomic and proteomic advances; and address the role of SWI/SNF in human diseases, including cancer and viral infections. These studies have greatly increased our understanding of complex nuclear processes.

DNA storage and chromosome packaging are important biological processes common to all living organisms. In eukaryotes, the advent of nucleosome-based DNA organization not only promoted favorable packing ratios that increase cellular DNA content but also facilitated the development of complex regulatory mechanisms. Inherent to any packing solution is the need for reversibility, as DNA must remain accessible to cellular machinery as required. Chromatin-remodeling proteins form crucial complexes that reposition nucleosomes to accomplish this task.

SWI/SNF (s̲wi̲tch/s̲ucrose n̲onfermentable) was the first ATP-dependent chromatin-remodeling complex to be described; however, its full recognition was initially obscured by the pleiotropic phenotypes that resulted when genes encoding several of its subunits were mutagenized in diverse screens. These phenotypes in *Saccharomyces cerevisiae* included the ability to undergo mating-type switching (1), increased mutation rates of mtDNA (2), and regulation of invertase gene expression in sugar metabolism (3). Since these initial studies nearly 3 decades ago, SWI/SNF has emerged as the archetypical and best characterized ATP-dependent chromatin remodeler, yet many aspects of its biology are only beginning to be defined.

Here, we review SWI/SNF biochemistry; highlight recent genomic and proteomic analyses of composition and function; and address the role of SWI/SNF in human diseases, including cancer and viral infections. Numerous integrative approaches and diverse methodologies have been applied to SWI/SNF (Table 1). Although SWI/SNF complexes from different organisms share many commonalities, there are also many attributes unique to a particular organism; this minireview focuses on human SWI/SNF, for which many recent advances have occurred. In particular, large-scale data from ENCODE (4) and various cancer sequencing projects are useful for determining functional genomic elements and disease states associated with SWI/SNF components.

Overview of SWI/SNF Complexes

The SWI/SNF family of chromatin remodelers spans eukaryotic lineages; however, the compositional details of these complexes vary, as evident by comparing yeast and mammalian models (Fig. 1). Purified SWI/SNF complexes contain 10–12 polypeptides and have an apparent molecular mass of ∼2 MDa in mammals (5) and 1.14 MDa in yeast (6). Central to SWI/SNF function is a DNA-dependent ATPase named Snf2p in yeast, which led to the recognition of the SNF2 subfamily of ATPases (7–9). SWI/SNF complexes in mammalian cells contain one of two possible ATPases (Brg1 or Brm) that are orthologous to yeast Snf2p.

Mounting evidence suggests that mammalian SWI/SNF has a large capacity for selected subunit substitutions, the contexts and consequences of which are only beginning to be elucidated. Human SWI/SNF subunits are often encoded by more than one gene, thus permitting combinatorial assembly and a diversity of related complexes, some of which are modulated during development and cell differentiation. Canonical human SWI/SNF complexes contain a single ATPase, a "core" group of subunits consisting of Ini1 (i̲ntegrase i̲nteractor 1̲), BAF155 (B̲rg1-a̲ssociated f̲actor), and BAF170, plus seven other accessory subunits, one of which is β-actin. Four of the accessory subunits are each encoded by a different gene family that has between two and four members, thus permitting 72 possible combinations among them when allowing for one protein from each family per SWI/SNF complex (10). BAF complexes contain either BAF250A or BAF250B, whereas PBAF (polybromo B̲rg1-a̲ssociated f̲actor) configurations instead contain BAF180 (11, 12). In contrast to the conventional distinctions between the BAF and PBAF complexes, recent biochemical evidence hints that some SWI/SNF complexes may actually contain both BAF180 and BAF250 (13). Specialized SWI/SNF complexes, such as those found in embryonic stem (ES)[2] cells, include Brg1, BAF155, and BAF60A but exclude Brm, BAF170, and BAF60C (14, 15). Thus, both cellular and developmental contexts are highly important when considering the composition of SWI/SNF, as well as its eventual targets and actions.

Notably, the majority of SWI/SNF subunits are capable of binding to DNA or chromatin. DNA-binding domains found among various SWI/SNF subunits include HMG, ARID (A̲T-rich i̲nteraction d̲omain), SANT, and Krüppel domains (10). Binding appears to lack sequence specificity; however, recognition of certain DNA structures may be favored, such as the minor groove of DNA (16, 17) and four-way helical junctions

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[2] The abbreviations used are: ES, embryonic stem; HPV, human papillomavirus; RTA, replication and transcription activator; HTLV-1, human T-lymphotropic virus type 1; LTR, long terminal repeat.

TABLE 1

Example methodologies and results from SWI/SNF studies

The results cited typically have multiple lines of supporting evidence in addition to the indicated method and experimental system. ER-α, estrogen receptor-α; ySWI/SNF, yeast SWI/SNF.

Approach	System	Results	Refs.
Chromatography, immunoaffinity purification, peptide sequencing	Various cell lines	Distinct Brg1- and Brm-containing complexes; heterogeneity in SWI/SNF complexes	5
Immunoprecipitation, MS	SWI/SNF subunits as bait in mouse ES and HeLa cells	Specialization of BAF complexes in ES cells; network of SWI/SNF-interacting proteins	15, 45
Western blot analyses	SWI/SNF subunits in various tumor cell lines	Some SWI/SNF subunits are missing or show reduced expression in the cell lines tested.	91
Immunohistochemistry	Human tumors of various types	Loss of Ini1 staining in malignant rhabdoid tumors	51
Loss-of-function analyses	Mouse knockout studies of Ini1	Ini1$^{-/-}$ mice do not recover; Ini1$^{-/-}$ embryos are peri-implantational lethal; and Ini1$^{+/-}$ mice are predisposed to cancer.	52–54
Chromatin fractionation	HeLa cells using lamin B as a marker	SWI/SNF is partially associated with the nuclear matrix.	36
3C	Murine fetal liver cells	Brg1 is necessary for chromatin looping in the α-globin locus.	39
Sequential chromatin immunoprecipitations, PCR	ER-α at the pS2/TFF1 promoter in MCF-7 cells	Binding kinetics of ER-α, SWI/SNF, and other factors	29
ChIP-seq	Brg1 in mouse ES cells; Brg1 in mouse CD4$^+$ T helper cells; Ini1, Brg1, BAF155, and BAF170 in HeLa cells	Genome-wide locations of SWI/SNF subunits; integration with other data types	43–45
Exome and targeted resequencing	Human tumors and cell lines of various malignant types	Somatic inactivating mutations in BAF250A/ARID1A, BAF200/ARID, BAF180, Brg1, and Brm	55–59, 61, 62
Yeast two-hybrid	Various reporter constructs	Interactions between Ini1 and HPV-18 E1, between Ini1 and EBNA2, and between Ini1 and HIV-1 integrase	74, 78, 82
Purification and immunoblotting of HIV-1 virions	HIV-1-infected cells of various types	Ini1 is found in HIV-1 virions, but Brg1, Brm, BAF155, and BAF170 are not.	84, 85
Immunofluorescence, confocal microscopy	HIV-1-infected CD4$^+$ HeLa cells	Partial redistribution of Ini1 from the nucleus to the cytoplasm in response to HIV-1	83
NMR spectroscopy, CD spectroscopy, isothermal calorimetry	Recombinant human Brg1 proteins; linear and four-way helical DNA substrates	Thermodynamic parameters of the HMG domain and the bromodomain from Brg1 in interactions with DNA	19
Site-directed mapping of histone-DNA contacts	Purified ySWI/SNF; modified Cys-53 of histone H2B	Model of translocation; SWI/SNF interaction with nucleosomes at superhelical location2 (SHL2)	37
Optical tweezers	Purified ySWI/SNF on a single nucleosomal template	Intranucleosomal looping, translocation rates, and force measurements	38

(18, 19). Epigenetic modifications also contribute to SWI/SNF and chromatin associations. Bromodomains, found in both of the ATPases and in several other SWI/SNF subunits, are thought to recognize acetylated lysines in histones (20). BAF155 and BAF170 each contain a chromo-related domain, which suggests a high affinity for methylated histones (21). Plant homeodomains in BAF45 are similarly suspected of interpreting particular histone modifications (22). Several SWI/SNF subunits can occur in an E3 ubiquitin ligase complex that monoubiquitinates histone H2B at Lys-120 (23), a modification that is associated with highly transcribed genes and is thought to promote efficient transcriptional elongation (24). It stands to reason that the chromosomal targeting of SWI/SNF is rendered more flexible by its wide spectrum of substrates and the ability of its subunits to bind both DNA and modified histones.

Recruitment of SWI/SNF

One of the great mysteries and areas of research for SWI/SNF, as well as for large diverse protein complexes in general, is how they are recruited to and assemble on DNA. Affinities of chromatin-associated factors depend on the underlying DNA sequence; the local chromatin environment; and other complexities, such as tissue type, cell cycle, and developmental stage. In the formation of productive SWI/SNF complexes, stochastic assembly and transient interactions among subunits may also play a significant role, as has been proposed for other large protein complexes, such as RNA polymerases and associated transcription factors (25), spliceosomes (26), and DNA repair complexes (27).

The DNA-binding abilities of certain SWI/SNF subunits are suggestive of one means of recruitment. Additionally, SWI/SNF can be targeted to DNA by transcription factors, resulting in either transcriptional activation or repression (28). In one variation on this theme, SWI/SNF targeting occurs cyclically through its association and dissociation with nuclear receptors. Two well documented examples include estrogen receptor-α (29) and the glucocorticoid receptor (30). In another mode of transcriptional activation, SWI/SNF may prime some promoters for rapid induction, as has been observed with interferon signaling (31).

The actions of SWI/SNF are not isolated from other regulatory proteins, as many of these large complexes interact with the same genomic regions, where they influence one another. As noted below, histone- and DNA-modifying enzymes co-purify substoichiometrically with SWI/SNF and, as determined by ChIP, have been found at the same genomic locations as SWI/SNF. Concentration of critical transcription-related proteins into factories has been proposed and would facilitate efficient gene expression, often utilizing the same machinery for multiple promoters (32, 33). This is accomplished by DNA looping, which brings distant regions of chromatin into close proximity,

FIGURE 1. Subunits of *S. cerevisiae* and human SWI/SNF complexes.

yeast SWI/SNF	yeast RSC	human BAF	human PBAF
Snf2/Swi2 (1,703)	Sth1 (1,359)	BAF250A (2,285)	BAF200 (1,835)
Swi1/Adr6 (1,314)	Rsc1 (928)	BAF250B (2,236)	BAF180 (1,689)
Snf5 (905)	Rsc2 (889)	Brg1 (1,647)	Brg1 (1,647)
Swi3 (825)	Rsc3 (885)	Brm (1,590)	BAF170 (1,214)
Swp82 (623)	Rsc30 (883)	BAF170 (1,214)	BAF155 (1,105)
Snf12/Swp73 (566)	Rsc4 (625)	BAF155 (1,105)	BAF60A (515)
Arp7 (477)	Rsc9 (581)	BAF60A (515)	BAF60B (531)
Arp9 (467)	Rsc8 (557)	BAF60B (531)	BAF60C (483)
Snf6 (332)	Rsc58 (502)	BAF60C (483)	BAF57 (411)
Taf14 (244)	Rsc6 (483)	BAF57 (411)	BAF53A (429)
Snf11 (169)	Arp7 (477)	BAF53A (429)	BAF53B (426)
Rtt102 (157)	Arp9 (467)	BAF53B (426)	Ini1/BAF47 (385)
	Rsc7/Npl6 (435)	Ini1/BAF47 (385)	BAF45A (498)
	Sfh1 (426)	BAF45A (498)	BAF45B (380)
	Ldb7/Rsc14 (180)	BAF45B (380)	BAF45C (378)
	Rtt102 (157)	BAF45C (378)	BAF45D (391)
	Htl1 (78)	BAF45D (391)	β–actin (375)
		β–actin (375)	

Each *box* represents a SWI/SNF subunit that is encoded by a separate gene. In *S. cerevisiae*, the SWI/SNF family encompasses both its namesake, yeast SWI/SNF, and the closely related but more abundant RSC (remodeling the structure of chromatin) complex, which has different roles from yeast SWI/SNF (92–94). In humans, the SWI/SNF family includes both the BAF and PBAF subclasses. The number of amino acids in the longest isoform is shown in *parentheses*. Subunits that share homology or that are closely related in function are shown in the same color. The *braces* grouping multiple subunits indicate that only one of the individual subunits is present in a given complex. Not all subunits are present in all tissues, and additional subunits and complexes that are tissue-specific are likely to be discovered. BAF250A, BAF250B, and BAF200 are also known as ARID1A, ARID1B, and ARID2, respectively.

and by ensuring that each factory has an adequate concentration of factors necessary for transcription. In this regard, SWI/SNF may also drive transcription by contributing to the formation of long-range interactions and by cooperative binding with other factors (34).

Facilitation of DNA Looping by SWI/SNF

Numerous biophysical studies have been performed to characterize the topology and dynamics of SWI/SNF. Although the literature discusses many insightful structural and mechanistic models (reviewed in Ref. 35), for brevity, we focus on looping due to its potential role in mediating both short- and long-range genomic interactions. DNA looping is relevant to SWI/SNF complexes on three scales: 1) within a nucleosome; 2) between nearby nucleosomes, thus creating a loop of intervening DNA (36); and 3) in macromolecular assemblies that bridge genomic regions though long-range interactions that occur over many kilobases. On the intranucleosomal scale, DNA looping is often postulated as an intermediate step during the SWI/SNF chromatin-remodeling process. *In vitro* and single-molecule approaches have been central to illustrating how SWI/SNF may operate, with several studies indicating the formation of intranucleosomal loops of ~50–100 bp (37, 38).

On a larger, chromosomal scale, DNA looping plays a significant role in gene regulation on a system-wide level by bringing linearly distant regions into close spatial proximity. Chromosomal looping interactions have been mapped at high resolution *in vivo* using 3C (chromosome conformation capture) and related methods. Most of the knowledge we have to date about

these interactions is limited to loci that were specifically targeted for investigation, but more large-scale studies are forthcoming (34). Examples of SWI/SNF-mediated higher order chromatin interactions are loops that form in the β-globin locus control region (39), in the α-globin locus (40), throughout regions of the 200-kb T helper 2 (T_h2) cytokine locus (41), and across the 150-kb *CIITA* locus (42).

Genomic Approaches to SWI/SNF Characterization

The combination of ChIP with either DNA microarrays (ChIP-chip) or, more recently, sequencing (ChIP-seq) enables the genome-wide localization of chromatin-associated proteins. Several recent studies highlight the use of a genomic approach in elucidating regulatory regions associated with SWI/SNF localization patterns. In the first of two studies conducted in mouse cells, Brg1- and BAF155-binding regions were identified by ChIP-seq in ES cells, and the resulting occupancies were compared with previously published locations of transcription factors known to be critical to stem cell differentiation, including Oct4, Sox2, and Nanog. Not only was there significant colocalization between Brg1 and these transcription factors, but shRNA-mediated knockdown of Brg1 led to the elevated expression of many developmental and ES-specific genes, indicating an important role for Brg1 as a repressor. Such repression by SWI/SNF was hypothesized by the authors to be necessary for blocking premature differentiation (43). In a second study, the authors isolated primary cells from mice and examined Brg1 localization patterns by ChIP-seq, this time over a developmental course, progressing from naïve to differentiated and stimulated $CD4^+$ T helper cells. Brg1-associated peaks were more numerous and showed stronger levels in the T helper cells that had undergone both differentiation and activation and were also found to be positively correlated with gene activity and induction (44).

In a third study, ChIP-seq was applied to BAF155, BAF170, Ini1, and Brg1 in HeLa cells with an emphasis on integrating data from multiple experiment types (all determined in HeLa cells), including regions associated with transcription, RNA polymerases II and III, CTCF (<u>CCCTC</u>-binding <u>f</u>actor), predicted enhancers, lamins A/C and B, DNA replication origins, and domains associated with the H3K27me3 histone modification. Strikingly, certain combinations of the SWI/SNF subunits were associated with transcripts that had higher expression levels, whereas other combinations were associated with transcripts with lower expression levels. When all possible combinations of BAF155, BAF170, Ini1, and Brg1 are considered, the greatest levels of transcription are associated with four different configurations: 1) the complete core of Ini1, BAF155, and BAF170; 2) the complete core plus Brg1; 3) Ini1 and BAF155 only; and 4) Brg1, BAF155, and BAF170. Overall, Brg1 appeared to have a dampening effect on transcription levels in the absence of two or more of the accessory subunits. The loss or hijacking of SWI/SNF subunits in a disease context would be profound in light of these transcriptional variations. In surveying the ENCODE pilot regions (~1% of the genome) where data exist for those genomic regions associated with replication origins and with the nuclear lamina, 32% of SWI/SNF regions co-occur with replication origins, and 40% of SWI/SNF regions
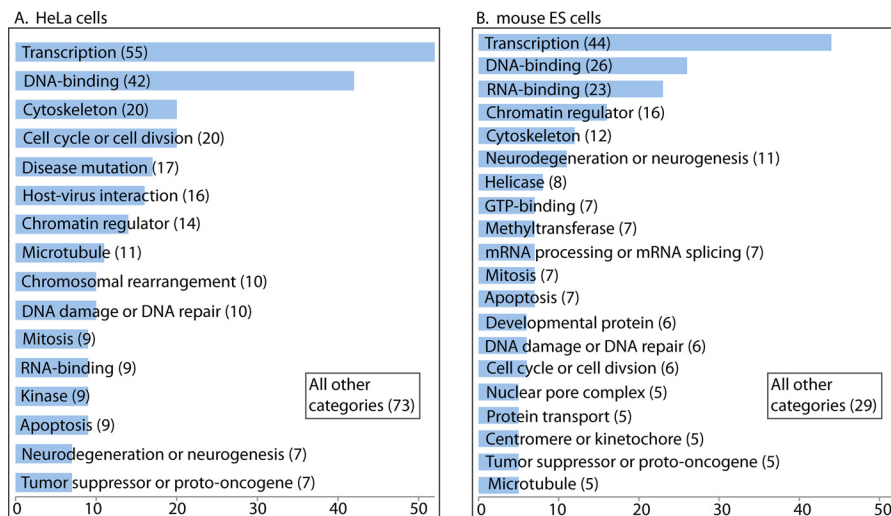
A. HeLa cells

Transcription (55)
DNA-binding (42)
Cytoskeleton (20)
Cell cycle or cell divsion (20)
Disease mutation (17)
Host-virus interaction (16)
Chromatin regulator (14)
Microtubule (11)
Chromosomal rearrangement (10)
DNA damage or DNA repair (10)
Mitosis (9)
RNA-binding (9)
Kinase (9)
Apoptosis (9)
Neurodegeneration or neurogenesis (7)
Tumor suppressor or proto-oncogene (7)

All other categories (73)

0 10 20 30 40 50

B. mouse ES cells

Transcription (44)
DNA-binding (26)
RNA-binding (23)
Chromatin regulator (16)
Cytoskeleton (12)
Neurodegeneration or neurogenesis (11)
Helicase (8)
GTP-binding (7)
Methyltransferase (7)
mRNA processing or mRNA splicing (7)
Mitosis (7)
Apoptosis (7)
Developmental protein (6)
DNA damage or DNA repair (6)
Cell cycle or cell divsion (6)
Nuclear pore complex (5)
Protein transport (5)
Centromere or kinetochore (5)
Tumor suppressor or proto-oncogene (5)
Microtubule (5)

All other categories (29)

0 10 20 30 40 50

FIGURE 2. **Histograms showing the frequencies of UniProt keywords for proteins that co-purify with SWI/SNF factors.** The keywords shown were retrieved from the UniProt Database for proteins that co-purify with a SWI/SNF factor for HeLa cells (*A*; data taken from Table S10 in Ref. 45) and mouse ES cells (*B*; data taken from Table S1 in Ref. 15). Multiple keywords may be associated with a single protein.

co-occur with lamin-associated regions (45). These observations are consistent with the view that the genomes of higher eukaryotes are non-randomly organized with respect to the positioning of chromosomes and genes (46, 47) and with a previous study showing that a fraction of SWI/SNF co-purifies with the nuclear matrix (48).

From these three ChIP-seq studies of SWI/SNF subunits, one can begin to form a genomic view of SWI/SNF chromosomal associations. All three studies found similar numbers of regions enriched for Brg1: 10,559 regions in mouse ES cells; 7,577–18,766 regions in mouse CD4$^+$ T helper cells, depending upon the degree of differentiation and stimulation; and 12,317 regions in HeLa cells. The footprints of these regions for Brg1 were more variable, with a median peak length of 6,200 bp in ES cells, a median length of 1,108 bp in HeLa cells, and a mean length of 170 bp in CD4$^+$ T helper cells. These differences may reflect the fact that each of the studies used a different peak calling algorithm and may also reflect intrinsic experimental variability. Across all three studies, many Brg1 regions were either intergenic or distal to transcriptional start sites (43–45). In HeLa cells, the union of all regions for Ini1, BAF155, BAF170, and Brg1 resulted in 49,555 "high-confidence" SWI/SNF regions; 90% co-occurred with some combination of a 5′-end of a protein-coding gene, an RNA polymerase II-associated region, a CTCF site, and/or a predicted enhancer, suggesting that SWI/SNF co-occurs with many different types of functional regions (45). Similar conclusions were drawn in the CD4$^+$ T helper cell study, as Brg1 binding was found to overlap with subsets of enhancers, locus control regions, cohesin-binding sites, and DNase I-hypersensitive sites, all of which had been previously identified in T helper cells (44).

Proteomic Approaches to SWI/SNF Characterization

Global characterizations of SWI/SNF are not comprehensive without the addition of proteomic data, and such large-scale data sets are complementary to genomic approaches. Not only are MS-based techniques for the analysis of protein complexes invaluable for the discovery of novel SWI/SNF partners, but they also can be used as part of an antibody validation procedure for determining whether an antibody of interest is "ChIP-grade," thereby encouraging genomic and proteomic experiments to be performed in tandem. Immunoprecipitated proteins from non-cross-linked HeLa cells were identified by MS for six different SWI/SNF subunits: Brg1, Brm, Ini1, BAF155, BAF170, and BAF250A. Comprehensive analysis of SWI/SNF-interacting proteins revealed the presence of transcription factors, DNA repair proteins (ERCC5 and RAD50), DNA replication proteins (MCM2 and RPA1), and proteins important for chromosome integrity (NUF2, BUB1B, CENP-E, and PTTG1) (45). In total, 158 SWI/SNF-interacting proteins have been described in HeLa cells across numerous studies from multiple investigators (45), and ~200 SWI/SNF-interacting proteins have been described in mouse ES cells, including histone- and DNA-modifying enzymes and regulators (*e.g.* HDAC1, JARID2, DNMT3b, and DNMT3L) (Fig. 2) (15).

Characterization of SWI/SNF complexes has benefited from proteomic approaches even when SWI/SNF was not the subject of investigation because its subunits have been identified both serendipitously and as prey in other studies. *DPF3* (now also known as *BAF45C*) was identified as a novel gene of unknown function that was significantly up-regulated in congenitally malformed human hearts. Subsequent MS identification of DPF3-binding partners revealed that DPF3/BAF45C is a constituent of SWI/SNF in cardiac tissue and co-occurs with another cardiac enriched SWI/SNF subunit, BAF60C (49).

SWI/SNF and Cancer

Mutations in several of the subunits comprising SWI/SNF have been linked to malignant transformation and progression. The first recognition of a tumor suppressor role for a SWI/SNF subunit emerged with the discovery of truncating mutations in Ini1 in malignant rhabdoid tumors, which occur in early childhood, have a poor prognosis, and are found predominantly in the central nervous system and kidneys (50, 51). In mouse models, Ini1 heterozygotes (Snf5$^{+/-}$) develop tumors resembling

human malignant rhabdoid tumors (52–54) upon loss of the remaining wild-type allele.

Characterizations of additional types of malignant cells have revealed mutations or altered expression levels of other SWI/SNF subunits. For example, two independent studies, both of which used exome sequencing, found somatically acquired inactivating mutations in BAF250A in ovarian clear cell carcinomas (57% or 24 of 42 cases tested (55) and 46% or 55 of 119 cases tested (56)). BAF250A somatic non-silent mutations are also relatively common in transitional cell carcinoma of the bladder (12% or 12 of 97 cases tested by exome sequencing (57)). Other exome sequencing projects have uncovered somatic inactivating mutations in BAF200 in hepatitis C virus-associated hepatocellular carcinomas (18% or 6 of 33 cases tested (58)) and in BAF180 in clear cell renal carcinomas (41% or 92 of 227 cases tested (59)). Interestingly, both of the SWI/SNF ATPases appear to be associated with lung cancer, as 10% (6 of 60) of non-small cell lung carcinomas stained negatively for both Brg1 and Brm, and all six of these patients had poor survival compared with stage-matched ATPase-positive tumors (60). Sequencing of the Brg1-coding region in 59 lung cancer cell lines demonstrated that 14 of them (24%) carried inactivating mutations in Brg1, and cell lines of the non-small cell lung cancer type were significantly more likely to be affected (13 of 37, 35%) (61).

As illustrated above, sequence analysis of exonic regions can be highly informative in the characterization of cancer genomes; however, mutations in noncoding regions may also have severe consequences. Two different short insertions in the *Brm* promoter region can lead to *Brm* silencing in the absence of additional mutations in the coding region. The homozygous presence of both of these variants appears to be common in Brm-negative non-small cell lung carcinomas (8 of 10 primary tumors tested), and furthermore, among smokers, there is an increased risk of lung cancer when both of these promoter polymorphisms are present homozygously (62).

Thus, the analyses of clinical data and patient-derived samples illustrate several points. First, various SWI/SNF subunits have tumor suppressor roles; and second, each of the mutated subunits appears to be associated with its own set of neoplasms. As more cancer genomes are sequenced, the ascertainment of mutations should assist in the differential diagnoses of tumor types, *e.g.* atypical teratoid/rhabdoid tumors show loss of Ini1 expression by immunohistochemistry, whereas other seemingly related tumor types do not (51).

Exactly how mutations in SWI/SNF subunits lead to malignant transformation remains enigmatic, as multiple mechanisms are conceivable. Much attention over the years has been focused on the contributions of SWI/SNF to regulating gene expression. As noted above, SWI/SNF complexes are multifaceted in their compositions and their associations. Consequently, mutations in a particular SWI/SNF subunit may disrupt the combinatorial assemblies and targeting of the remaining SWI/SNF complexes. Among the transcription factors known to interact with SWI/SNF are the products of tumor suppressor genes and proto-oncogenes, including BRCA1, c-Myc, Rb, and p53, as well as steroid receptors (reviewed in Ref. 63). Aberrant gene expression due to loss of normal SWI/

SNF function may also lead to disease progression, as its chromatin-remodeling activity is important in cytokine signaling, differentiation, pluripotency, and self-renewal (63–65). With regard to Ini1, several groups have surveyed differential gene expression in rhabdoid tumors relative to normal tissues and other tumor types and have uncovered candidate biological processes and pathways, such as Hedgehog signaling (66), Polycomb silencing (67), developmental processes and neurogenesis (68), and interferon signaling (69).

In addition to changes in transcriptional regulation and epigenetics following mutations in SWI/SNF, several other studies indicate a role for SWI/SNF in genome stability. For example, SWI/SNF plays a role in DNA repair (70) and DNA replication (71) and is found at centromeres in both yeast and humans. In *S. cerevisiae*, the catalytic subunit of SWI/SNF, Snf2p, is enriched at centromeres and is thought to contribute to the proper localization of the centromeric histone variant Cse4p (or CENP-A, as it is known in higher eukaryotes) (72). Brg1-deficient mice show dissolution of pericentromeric heterochromatin domains (73). In mammalian cells, BAF180, the signature subunit of PBAF, has been similarly observed at kinetochores, as well as at spindle poles (11). These observations highlight the diverse roles of SWI/SNF in chromosomal biology.

SWI/SNF and Oncogenic Viruses

The relationship between SWI/SNF and its diverse roles in the cause and progression of cancer becomes even more complex when considering that various SWI/SNF subunits interact with proteins from oncogenic viruses. The chromatization of viral DNA implies that it has many of the same epigenetic layers as the host DNA, and hence, the appropriation of SWI/SNF may be important in overcoming barriers to viral transcription and replication. For example, a series of experiments utilizing co-immunoprecipitations, two-hybrid assays, and mutagenesis with human papillomavirus (HPV) have shown that 1) the HPV-18 E1 protein, which binds to the viral origin of replication, interacts with Ini1 (74); 2) the HPV-18 E2 transcriptional regulator associates with both Ini1 and Brg1 (75); and 3) the HPV-16 E7 protein, which promotes cell cycle progression, binds to Brg1. These interactions have *in vivo* consequences, as Ini1 and Brg1 stimulate HPV DNA replication and deregulate the expression of E7-mediated genes (76).

Two genetically related herpesviruses, Epstein-Barr virus and Kaposi sarcoma-associated herpesvirus, both recruit SWI/SNF subunits but by apparently distinct mechanisms. Among all known gammaherpesviruses, the replication and transcription activator (RTA) protein is evolutionarily conserved, particularly in its N-terminal DNA-binding domain. The RTA Kaposi viral homolog recruits SWI/SNF, as shown by MS analysis of RTA-binding proteins. The interaction between RTA and SWI/SNF appears to be mediated through Brg1 and the C terminus of RTA and is abolished by mutations in conserved residues of RTA (77). Intriguingly, an interaction between the Epstein-Barr virus homolog of RTA and SWI/SNF has not been reported; however, the Epstein-Barr virus nuclear antigen EBNA2, which plays a crucial role in B-cell transformation and immortalization, binds Ini1 (78, 79).

The Tax1 oncoprotein encoded by human T-lymphotropic virus type 1 (HTLV-1) interacts with Brg1, BAF155, BAF57, and BAF53 (80). Not only do viral proteins associate with SWI/SNF subunits, but also various SWI/SNF subunits are differentially expressed in virally infected cells. Uninfected T-cells have low levels of BAF170 protein, whereas BAF170 is well expressed in both HTLV-1-infected cells and HIV-1-infected cells. Additionally, BAF155 and BAF60 proteins show decreased levels in HTLV-1-infected T-cells but not in uninfected or HIV-1-infected T-cells (81). Future studies should investigate whether infection of primary T-cells with either the HTLV-1 or HIV-1 retrovirus results in the same effects that were observed in the cancer cells used in these expression assays.

SWI/SNF and HIV-1

By pillaging host machinery, viruses succeed in adapting parts and processes to their own ends. As gatekeepers to the genome, chromatin-remodeling complexes are vulnerable in this regard. Two-hybrid screens for proteins interacting with HIV-1 integrase led to the cloning of human SNF5, also known as Ini1. Depending on the ratio of Ini1 to integrase, recombinant Ini1 can either stimulate or inhibit integrase-joining activity *in vitro* (82), yet whether this relates to *in vivo* activity is unresolved.

Interactions between Ini1 and HIV-1 take place in both the nucleus and the cytoplasm. Cytoplasmic interactions between Ini1 and HIV-1 proteins occur during both early and late phases of the viral cycle. Upon infection of either CD4$^+$ HeLa cells or primary T-cells with HIV-1, a fraction of Ini1 redistributes from the nucleus to the cytoplasm, where it co-localizes with HIV-1 pre-integration complexes. This effect is specific to Ini1 and is transient; Brm and BAF155 remain in the nucleus, and the nuclear localization of Ini1 is restored within 10 h (83). Curiously, Ini1 is packaged into mature HIV-1 virions, but Brg1 and BAF155 are not (84). The incorporation of Ini1 into HIV-1 virions and its interaction with HIV-1 integrase are specific because these phenomena are not observed with either HIV-2 or simian immunodeficiency virus (85).

Of particular interest is the mechanism of HIV-1 transcription prior to the production of Tat protein because a pivotal point in viral replication is the switch to up-regulation of the Tat transactivator and consequently the entire HIV-1 genome (86). SWI/SNF has been implicated in transcription of the HIV-1 genome during both basal and Tat-amplified phases of expression from the long terminal repeat (LTR) promoter. Multiple researchers have detected interactions between Tat and various SWI/SNF components, including BAF155, BAF170, and the Brg1 and Brm ATPases. Additionally, Brm, Brg1, and BAF155 have been observed by ChIP to be present at the LTR promoter, and recruitment of SWI/SNF to the LTR promoter is enhanced by acetylated Tat (87–90).

Concluding Remarks

Several themes emerge from the studies summarized above. First, SWI/SNF complexes are heterogeneous, and many novel forms likely remain to be discovered as more tissue types are examined. Second, SWI/SNF has roles and interactions beyond transcription, leading one to ask if SWI/SNF or several of its
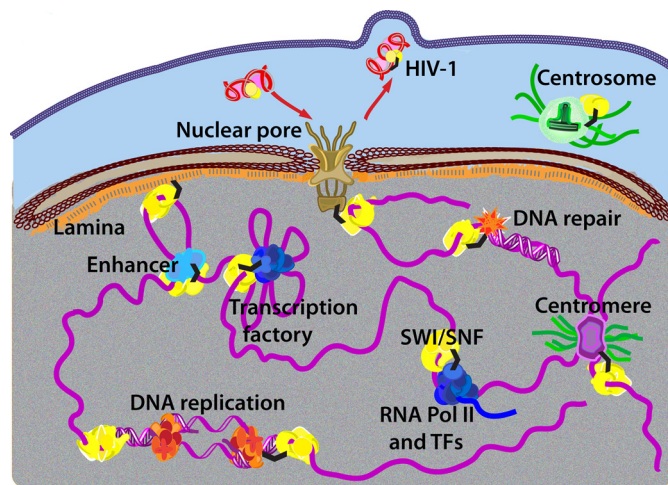

FIGURE 3. **Speculative representation of SWI/SNF roles and interactions.** The interactions displayed (*black chevrons*) are derived from multiple data types, particularly as summarized in Refs. 45 (Table S10), 15 (Table S1), and 83–84. SWI/SNF subunits are shown in *yellow*. For simplicity, an intact nucleus is shown. In addition to the known transcriptional roles of SWI/SNF, it may also participate in chromatin and nuclear organization. All of these functions have potential disease implications. *RNA Pol II*, RNA polymerase II; *TFs*, transcription factors.

subunits may affect processes besides chromatin remodeling (Fig. 3). SWI/SNF subunits play important roles in multiple parts of various viral life cycles and occasionally may be operating independently of other SWI/SNF components. Ini1 and Brg1 have been extensively characterized, which could be due to either promiscuity or ascertainment bias. Also, many cell lines favored for research carry mutations in SWI/SNF, which can alter complex composition (5, 91). As chromatin-occupied regions are identified for multiple factors and the data types are expanded to include transcribed regions, histone modifications, methylation patterns, and even regions involved in nuclear structure or DNA replication, a myriad of possibilities emerges for data integration. Additional connections among data types can be further achieved by including proteomic approaches to determine protein-protein interactions and post-translational modifications. Ultimately, such data integration will result in a rich view of overlapping nuclear processes and ensuing networks.

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