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Review

Diverse functions of ATP-dependent chromatin remodeling complexes in development and cancer

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Mammalian SWI/SNF like Brg1/Brm associated factors (BAF) chromatin-remodeling complexes are able to use energy derived from adenosine triphosphate (ATP) hydrolysis to change chromatin structures and regulate nuclear processes such as transcription. BAF complexes contain multiple subunits and the diverse subunit compositions provide functional specificities to BAF complexes. In this review, we summarize the functions of BAF subunits during mammalian development and in progression of various cancers. The mechanisms underlying the functional diversity and specificities of BAF complexes will be discussed.

Keywords ATP-dependent chromatin remodeling; SWI/SNF; BAF; development; cancer

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Epigenetic Regulation of Transcription During Development

During development, stem cells either self-renew to maintain and enlarge the stem cell pool or differentiate into different cell lineages. As stem cells gradually lose differentiation potential, become lineage-restricted progenitors, and finally adopt various cell fates, specific gene expression patterns determine the unique physiological states of individual cell types [1,2]. The establishment and maintenance of the transcription profiles in different cells require specific epigenetic landscapes. In the nucleus, DNA exists in the form of chromatin and the highly compact chromatin structure physically blocks the access of transcription factors and nuclear machinery to regulatory regions [3]. The repressive chromatin structures have to be overcome for active transcription to occur. Specific chromatin states could determine the expression competence of a gene.

Transcription factors and chromatin-regulating factors work in concert to build a chromatin environment that directs the expression of a distinct set of genes in each cell [4–6]. Moreover, the chromatin structures are dynamic and can be changed in response to developmental cues, extracellular signals or stress, which then direct the corresponding gene expression changes [7–9]. During development, lineage specification is accompanied by genome-wide chromatin re-organization and gene expression pattern changes. Reprogramming of differentiated cells to pluripotent stem cells or other lineages by defined transcription factors require global changes of epigenetic states [10,11]. Thus, epigenetic regulation at the chromatin level plays an important role during development and adult homeostasis. Mutations or alterations of epigenetic regulators and chromatin modifications cause developmental diseases and cancers.

There are four main types of epigenetic regulations at the chromatin level: DNA methylation, histone modification, adenosine triphosphate (ATP)-dependent chromatin remodeling, and the recently discovered non-coding RNAs [6]. During transcription regulation, transcription factors often engage more than one epigenetic mechanism to ensure precise transcription outcomes. Mediated by protein–protein interactions, there is significant crosstalk among different chromatin regulating factors. ATP-dependent chromatin-remodeling complexes (remodelers) regulate gene expression by destabilizing nucleosome structures to change the accessibility of DNA to transcription factors [12,13]. Chromatin-remodeling complexes can be divided into four groups, characterized by core ATPase subunits. Based on the defining ATPase, they are referred to as the SWI/SNF, ISWI, CHD, and INO80 families of remodelers [13,14]. Each family plays genetically non-redundant roles in regulating chromatin structures. In this review, we will focus on the SWI/SNF family, a group of prototypical ATP-dependent chromatin-remodeling complexes. Their diverse functions during mammalian development and cancer progression as well as the underlying molecular mechanisms will be discussed.

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Brg1/Brm-Associated Factors (BAF), A Mammalian SWI/SNF-like ATP-dependent Chromatin Remodeling Complex

Identification of SWI/SNF complexes

Like most chromatin regulating factors, ATP-dependent chromatin-remodeling factors exist in large multi-subunit complexes. The genes encoding the proteins that make up the prototypical ATP-dependent SWI/SNF chromatin-remodeling complex were identified in 1984 from two yeast genetic screens. These screens sought to identify the genes responsible for mating-type switch and sucrose-non-fermentable phenotypes [15,16]. Later biochemical and functional analyses indicated that many genes identified from the genetic screens such as Swi2/Snf2, Swi3, and Snf5 function coordinately to regulate the transcription of a large set of target genes [17]. They encode subunits of the million-dalton SWI/SNF complex, which can resist stringent purification conditions [18,19]. In this complex, the Swi2/Snf2 subunit has DNA-dependent ATPase activity, and it soon became clear that the yeast SWI/SNF complex regulates transcription by changing chromatin structures [20,21].

Following the identification of the yeast SWI/SNF complex, homologs of the SWI/SNF subunits in higher organisms were identified and corresponding complexes were biochemically purified. The *Drosophila* Swi2/Snf2 homolog Brahma (BRM) was identified as one of the trithorax group proteins, which antagonize the function of polycomb group (PcG) proteins in repressing homeobox gene expression [22]. Several other trithorax group proteins also turned out to be SWI/SNF subunits including OSA, MOR, and SNR1 [23–25]. Based on homology with *Drosophila* BRM, two genes in mammals were cloned that encode the Swi2/Snf2 homologs hBrm and Brm-related gene 1 (Brg1). When fused with a DNA-binding domain, both activated transcription [26,27]. hBrm also activated steroid receptor-mediated transcription [27]. When the ATPase domain of the yeast Swi2/Snf2 protein was replaced with that of human Brg1, the chimeric protein rescued the Swi2 null phenotype [26]. Using an antibody against both Brg1 and Brm, Wang *et al*. [28,29] affinity purified the mammalian SWI/SNF complexes and identified ~10 subunits. Later purifications from neural tissues and embryonic stem (ES) cells identified additional subunits [30–32]. Many SWI/SNF subunits are conserved from yeast to human, but significant differences also exist (**Table 1**).

As Brg1 and Brm are the two highly conserved ATPases of the mammalian SWI/SNF complexes, the mammalian complex is also referred to as BAF. In official nomenclature, the genes encoding BAF subunits are called SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin (Smarc) genes [85].

Biochemical activities of SWI/SNF complexes

The enzymatic subunit of the SWI/SNF complex is Swi2/Snf2, which contains an ATPase domain and a DEAD (Asp-Glu-Ala-Asp) box helicase domain. Swi2/Snf2 has no helicase activity, but does have DNA/chromatin-dependent ATPase activities [21,86]. In the presence of DNA or *in vitro* assembled chromosomes, recombinant Swi2/Snf2 or purified SWI/SNF complexes effectively hydrolyze ATP. A point mutation from lysine to arginine in the nucleoside-triphosphate (NTP) binding pocket of Swi2/Snf2 abolishes the ATPase activity [18,21]. In yeast, mutations in histones and histone modification enzymes were identified suppressing SWI/SNF mutation phenotypes, suggesting a genetic interaction between the SWI/SNF complex and chromatin [20,87]. *In vitro* and *in vivo* data illustrate that SWI/SNF complexes activate transcription by modulating chromatin structures using energy derived from ATP hydrolysis [86,88]. Nucleosomes in chromatin can be remodeled by SWI/SNF complexes in two general ways: by sliding along the DNA or by dissociation from chromatin [12]. Nucleosome distributions determine the DNA regions accessible to transcription factors and other nuclear proteins, and therefore SWI/SNF complexes regulate transcription and other nuclear activities such as recombination and DNA repair and replication.

Although most SWI/SNF subunits are required for the *in vivo* function of SWI/SNF complexes, Swi2/Snf2 protein alone is able to carry out nucleosome remodeling and nucleosome exchange activities *in vitro*. The addition of BAF47, BAF155, and BAF170 to Brg1 increases remodeling activity to a level comparable to that of the whole BAF complex. [89]. Thus, these subunits are considered core of the complex. The possible *in vivo* functions of other essential SWI/SNF subunits include, but are not restricted to, regulating the ATPase enzymatic activity of Swi2/Snf2 [89–91], maintaining complex integrity [92,93], targeting the complex to target genes by interacting with transcription factors [35,94–96], and recruiting other chromatin regulating factors [35,97–101], thus providing ATPase-independent chromatin-regulating activities. Therefore, the *in vivo* activities of the SWI/SNF complex must be much more complex than the available *in vitro* assays indicate and are context dependent. Therefore, assays reflecting SWI/SNF complex functions *in vivo* are urgently needed.

Originally, the chromatin-regulating activities of SWI/SNF complexes were thought to activate transcription. However, substantial evidence now indicates that SWI/SNF complexes, especially the mammalian BAF complexes, often function to repress transcription [35,41,42,102,103]. The transcription repression activities may be either ATPase dependent or independent [35,104]. The ATPase-dependent repression activities may involve remodeling nucleosomes to a repressive position to either inhibit the

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Table 1 Subunits of distinct BAF complexes and their functions in development and cancers.

Sub complexes	Yeast homolog	Fly homolog	Domain structures	Mammalian subunits	Developmental roles	Mutations or altered expression in primary tumors or cancer cell lines
Core subunits	Swi2/Snf2 Sth1	BRM	ATPase, Bromodomain, HSA, BRK	Brg1/Smarca4	Early embryonic development [33], zygotic genome activation [34], proliferation and/or differentiation of neurons [30,31,35], lymphocytes [36–40], heart [41–43], and blood cells [44,45]	~30% NSCLC [46–49], pancreatic [50], breast [51,52], prostate cancers [50,53], RTs [54], medulloblastoma [55]
				Brm/Smarca2	Brm null mice are ~15% larger than control [56]	Lung cancers [47,57]
	Swi3	MOR/BAP155	Chromo-related domain, SWIRM, SANT, Leu-zipper	BAF155/Smarcc1	Early embryonic development, heterozygotes display exencephaly [58], T cell maturation [40]	Increased expression in prostate cancers [59]
				BAF170/Smarcc2		
	Snf5	SNR1/BAP47	SNF5 domain	BAF47/SNF5/ Smarcb1	Early embryonic development [60–62], heterozygotes and mosaic deletion develop RTs and lymphoma [60–63]	98% RTs [64–66], Schwannomatosis [67], hepatoblastoma [68], undifferentiated and epitheliod sarcomas [69]
		BAP111	HMG, coiled-coil	BAF57/Smarce1	A dominant negative form causes T-cell differentiation defects [38]	Breast cancers [51,70]
	Swp73 Rsc6	BAP60	SWIB/MDM2 domain	BAF60a,b/ Smarcd1,2		
		d4	PHD, Krüppel, N-terminal	BAF45d/DPF2		
	β-actin	β-actin	Actin	β-actin		
npBAF	Arp4	BAP55	Actin-related protein	BAF53a/Actl6a	Required for neural progenitor proliferation [30]	
		SAYP	PHD, Krüppel	BAF45a/PHF10	Essential and sufficient for neural progenitor proliferation [30]	
nBAF	Arp4	BAP55	Actin-related protein	BAF53b/Actl6b	Required for activity-dependent dendritic growth [31]	
		d4	PHD, Krüppel, N-terminal	BAF45b/DPF1		

BAF	Swi1	OSA	ARID	BAF250a/ARID1a	Knockout mice die at E6.5, BAF250 null ES cells display defective proliferation and differentiation to mesoderm lineage [71]	50% ovarian clear cell carcinoma [72], 35% endometriod carcinoma [73], Medulloblastoma [55], bladder cancer [74]
				BAF250b/ARID1b	Knockout ES cells have differentiation defects [75]	
PBAF		BAP170	ARID, RFX, Zn finger	BAF200/ARID2		Hepatocellular carcinoma [76]
	Rsc1, Rsc2, Rsc4	polybromo	Bromodomain (6), BAH, HMG	BAF180/PBRM1	Required for cardiac chamber maturation and coronary development [77,78]	41% renal clear cell carcinoma [79], breast cancers [80]
		CG7154	Bromodomain	Brd7		Breast cancers [81]
CBAF	Swp73 Rsc6	BAP60	SWIB/MDM2 domain	BAF60c/Smarcd3	RNAi knockdown in embryos led to defects in heart morphogenesis [82]. Facilitate Gata4 and Tbx5 to induce heart tissue specification [83]	
		d4	PHD, Krüppel, N-terminal	BAF45c/DPF3	Required for heart and muscle development in zebrafish [84]	

binding of transcription activators or facilitate the binding of transcription repressors. The ATPase-independent activity may suppress gene transcription by recruiting DNA or histone modification enzymes. In addition, activation of certain genes by BAF complexes is also ATPase independent [35,104]. BAF complexes regulate a large set of target genes and the mechanisms appear to be highly context dependent. An ATPase-inactive *Brg1* mutant mouse with a point mutation knocked in at the *Brg1* locus has been generated and the comparison between the *Brg1* knockout and the ATPase-inactive *Brg1* knock-in mice in developing T cells indicates that Brg1 activation of CD4 gene transcription is ATPase independent [104]. As it is used to study other developmental processes, this mouse model will reveal other ATPase-dependent and -independent Brg1 functions.

Combinatorial assembly of mammalian BAF complexes

One feature unique to mammalian BAF complexes compared to the homologous complexes in lower organisms is that many of the BAF subunits are encoded by gene families [105]. So far, 14 BAF subunits, encoded by 25 genes, have been identified, and most BAF subunits have a broad range of expression. The general assembly rule is thought to be that each subunit position is occupied by one of the family members and different subunits can be combinatorially assembled. For example, the ATPase subunit could be either Brg1 or Brm, and the BAF 60 position could be occupied by BAF60a, b, or c. The only exceptions are BAF155 and BAF170, which are always present in the complex as homo- or hetero-dimers [29,32]. Thus, by combinatorial assembly, hundreds of BAF complexes with different subunit compositions could exist in the same cell. Certain BAF subunits have restricted expression patterns and thus could define tissue- or cell-type-specific BAF complexes. For example, neuron-specific BAF53b and BAF45b define the neuron-specific BAF (nBAF) complexes [31,106]; ES-cell-specific BAF (esBAF) complexes mainly contain Brg1 and BAF155, but not their homologs Brm and BAF170 [32,75]. BAF60c and BF45c are highly expressed in cardiocytes and form the basis of cBAF [107]. **Table 1** lists the known BAF subunits and summarizes some of their properties.

BAF complexes assembled from different sets of subunits potentially perform different functions. The first BAF complex to be shown to have a defined function was the PBAF complex. PBAF contains BAF180/polybromo and BAF200/ARID2, but not BAF250 subunits [108,109]. PBAF but not BAF250-containing BAF complexes are required for *in vitro* vitamin D receptor-mediated stimulation of transcription of a chromatin substrate [110]. The mechanisms underlying the functional differences of BAF and PBAF complexes remain unclear.

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The different subunit compositions of specific BAF complexes produce unique complex surfaces. Indeed, there are many different protein–protein interaction domains, histone modification recognition domains, and non-sequence-specific DNA-binding domains in BAF subunits (**Table 1**). These surfaces potentially mediate the interaction of BAF subunits with transcription factors, modified histones, and other chromatin-regulating factors in specific chromosome contexts. Thus, diverse BAF subunit compositions may underlie the recognitions of large but specific sets of BAF target genes and diverse biochemical mechanisms that regulate gene transcription.

Function of BAF Complexes in Stem Cells and During Development

BAF complexes play diverse roles during mammalian development. Deletions of genes encoding Brg1 and several other subunits in ES cells and in different developing tissues revealed extensive functions of BAF complexes in maintaining stem cell pluripotency, differentiation, and cell survival during development. Various phenotypes resulted from deletion of different subunits, reflecting specific functions of BAF complexes with different subunit compositions.

Involvement of BAF complexes in early embryonic development and ES cell pluripotency

Straight knockout of genes for several BAF core subunits caused similar early embryonic lethal phenotypes. Deletion of *Brg1*, *BAF155/Srg3*, or *BAF47/SNF5* led to similar peri-implantation death of the embryos [33,58,60–62]. Cultured $Brg1^{-/-}$ blastocysts did not hatch due to impaired inner cell mass development, suggesting that BAF complexes may be important for ES cell proliferation and/or differentiation [33].

In ES cells, the core transcription network of transcription factors Oct4, Nanog, and Sox2 regulate the expression of target genes important for maintaining ES cell pluripotency. Chromatin-regulating factors such as PcG proteins build a chromatin environment that prevents ES cells from differentiating, but allow the competence to adopt all cell fates in response to differentiation signals [1,2].

Using a proteomic approach, Ho *et al*. [32] purified BAF complexes from ES cells and determined the specific subunit composition for the BAF complex, termed as esBAF, which is defined by the presence of Brg1, BAF155, and BAF60a, and the absence of Brm, BAF170, and BAF60c. esBAF complexes function together with key transcription factors Oct4, Sox2, and Nanog in ES cells, participate in the core transcription circuitry, and coregulate their target genes [103]. esBAF complexes are required for the self-renewal and pluripotency of ES cells since knockdown using RNA interference (RNAi) or conditional deletion of *Brg1* or *BAF155* from ES cells significantly impairs proliferation and differentiation [111–113]. Knockout of *BAF250a* and *BAF250b* both impaired ES cell proliferation and altered differentiation potential but with significant differences. *BAF250a* knockout ES cells lost the ability to differentiate into mesoderm-derived cardiomyocytes and adipocytes, but not ectoderm-derived neurons. Consistent with this finding, $BAF250a^{-/-}$ mice fail to gastrulate or form mesoderms and die at ~E6.5 [71]. In contrast, deletion of *BAF250b* in ES cells led to downregulation of pluripotency genes, reduced proliferation, and increased expression of lineage-specific genes [75].

In a recent study, Ho *et al*. [114] analyzed the genome-wide function of esBAF complexes in regulating the Signal Transducers and Activators of Transcription protein (STAT) 3-mediated transcription in the leukemia inhibitory factor (LIF) signaling pathway. LIF/STAT signaling is important for maintaining the stemness of ES cells and preventing differentiation. Brg1 and LIF signaling coregulate a large set of target genes. Deletion of *Brg1* abolishes the binding of LIF effecter STAT3 to most target sites, suggesting the requirement of esBAF chromatin-remodeling activity for generating accessible STAT3 binding sites. Consistent with an antagonizing function between trithorax group and PcG proteins in fly, esBAF complexes also antagonize PcG binding to many Brg1-activated genes including many LIF target genes. Deletion of *Brg1* led to increased PcG binding to these genes, elevated levels of trimethylated histone 3 lysine 27 (H3K27me3), and decreased gene expression. Unexpectedly, for many genes known to be repressed by Brg1, *Brg1* deletion led to decreased PcG binding and decreased H3K27me3. Therefore, esBAF and PcG proteins do not simply antagonize each other. They can also synergistically repress gene expression to support ES cell pluripotency. However, the mechanisms governing the different BAF activity modes remain unclear.

The function of esBAF complexes in ES cell pluripotency is also indicated by their ability to enhance efficient reprogramming to gain pluripotency. Nuclear reprogramming of permeabilized somatic human cells using extracts from *Xenopus laevis* eggs and early embryos requires Brg1, demonstrating the importance of these complexes in the establishment of pluripotency [115]. Brg1 is required for zygotic genome activation [34], and it has been suggested that the depletion of Brg1 from enucleated zygotes may account for the failed nuclear reprogramming using enucleated interphase zygotes as recipients [116]. Importantly, esBAF complexes are able to facilitate induced pluripotent stem (iPS) cell formation. Overexpression of Brg1 and BAF155 significantly increases the efficiency of iPS formation induced by the Yamanaka factors (Oct4, Sox2,

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Klf4, and c-Myc). During reprogramming, esBAF complex components facilitate Oct4 binding to target promoters to initiate the ES cell transcription circuitry [117]. Thus, in ES cells and during reprogramming, the esBAF complex is an essential component of the core pluripotency transcriptional network and functions to initiate and maintain pluripotency.

Role of BAF complexes in neural development

The function of BAF complexes during neural development was first indicated by the exencephaly phenotypes of a fraction of *Brg1* and *BAF155/Srg3* heterozygous embryos [33,58]. Reduced levels of BAF complexes may cause unbalanced neural progenitor proliferation and differentiation or abnormal responses to certain signaling pathways that result in exencephaly. Studies of *Caenorhabditis elegans* T-cell asymmetric division demonstrated that *psa-1/Brg1* and *psa-4/BAF155* genes are required for asymmetric neurogenic divisions. Two temperature-sensitive mutations of these genes in worms generate fewer neurons and favor non-neuronal cell types [118]. In *Xenopus*, Brg1 is required for neuronal differentiation; it mediates the transcriptional activities of the proneural bHLH Neurogenin and NeuroD proteins [119].

During mammalian neural development, neural stem/progenitor cells can self-renew and have the potential to differentiate into all types of neuronal and glial cells. After adopting a neuronal cell fate, neurons develop specific features such as axons and dendrites and form elaborate synaptic connections. The dramatic differences between the natures of neural progenitors and neurons result from their specific gene expression patterns, the establishment, and maintenance of which require specific epigenetic environments [120–123].

The identification of BAF53b as a post-mitotic neuron-specific subunit suggests a specific neural function of certain BAF complexes [106]. A pioneering proteomic analysis of BAF complexes from developing neural tissues identified all the previously identified subunits except for BAF60b. In addition, a new family of proteins containing a Kruppel domain and double PHD fingers were identified as BAF subunits; these were designated BAF45a, b, c, and d [30,31]. Studies of BAF subunit expression revealed striking differences in expression patterns among several subunits including BAF53 and BAF45. In proliferating neural progenitors, BAF complexes contain BAF53a and BAD45a; whereas in post-mitotic neurons, levels of BAF53a and BAF45a are diminished and BAF53b and BAF45b are expressed. Thus, during the transition from multipotent, proliferating neural progenitors to differentiated post-mitotic neurons, BAF complexes exchange subunits from BAF53a and BAF45a to BAF53b and BAF45b; these complexes are termed as neural progenitor BAF (npBAF) and nBAF, respectively [30,31]. Using a series of elegant transgenic experiments, Yoo *et al.* demonstrated that the repression of *BAF53a* in post-mitotic neurons was mediated by two REST-regulated microRNAs (miRNAs), miR-9*, and miR-124. The two miRNAs recognize sequences in the 3′ UTR of *BAF53a* mRNA and represses its expression. Mis-expression of REST in post-mitotic neurons led to de-repression of *BAF53a*, indicating that the REST-regulated miRNAs direct the essential switch of chromatin regulatory complexes [124].

The significance of the subunit exchange of BAF complexes during neural development and the functions of npBAF and nBAF have been analyzed through multiple mutations. npBAF subunits are required for neural stem cell self-renewal and proliferation. Knockdown of *BAF45a* and *BAF53a* led to impaired neural progenitor proliferation, whereas expression of an exogenous *BAF45a* is sufficient to increase neural progenitor proliferation. Genetic deletion of the core subunit *Brg1* in neural progenitors led to defective neural stem cell self-renewal and maintenance, and impaired differentiation [30].

In post-mitotic neurons, nBAF complexes, defined by neuron-specific BAF53b and BAF45b/c subunits are required for activity-dependent dendrite growth. They regulate a transcription program important for neuron morphology and functions [31]. BAF53b is expressed in most if not all neurons. BAF53b and nBAF complexes have been shown to interact with calcium-responsive transcription coactivator (CREST) to regulate gene expression and dendrite outgrowth [31,125]. In addition, the identification of BAF53b-regulated developmental processes provided a genetic system to determine whether different subunits determine functional specificity of chromatin-regulating BAF complexes. Transgenic or overexpression of *BAF53b*, but not *BAF53a*, in *BAF53b*$^{-/-}$ neurons rescues neonatal lethality and activity-dependent dendrite growth defects, suggesting different functions of BAF53a and BAF53b despite the high degree of similarity between the two proteins [31]. In addition, mis-expression of *BAF53a* in neurons causes defective dendritic outgrowth, suggesting a dominant negative function of BAF53a in post-mitotic neuronal morphogenesis [124]. Thus, these studies provided *in vivo* evidences supporting the notion that combinatorial assembly of chromatin-remodeling complexes generates functional diversity.

During neural development, BAF complexes regulate various processes possibly mediated by many signaling pathways. Our recent studies of BAF functions in regulating the Sonic hedgehog (Shh) signaling pathway during neural development demonstrate how BAF complexes function in different developmental contexts [35]. Shh signaling plays diverse roles during animal development and adult tissue homeostasis through differential regulation of

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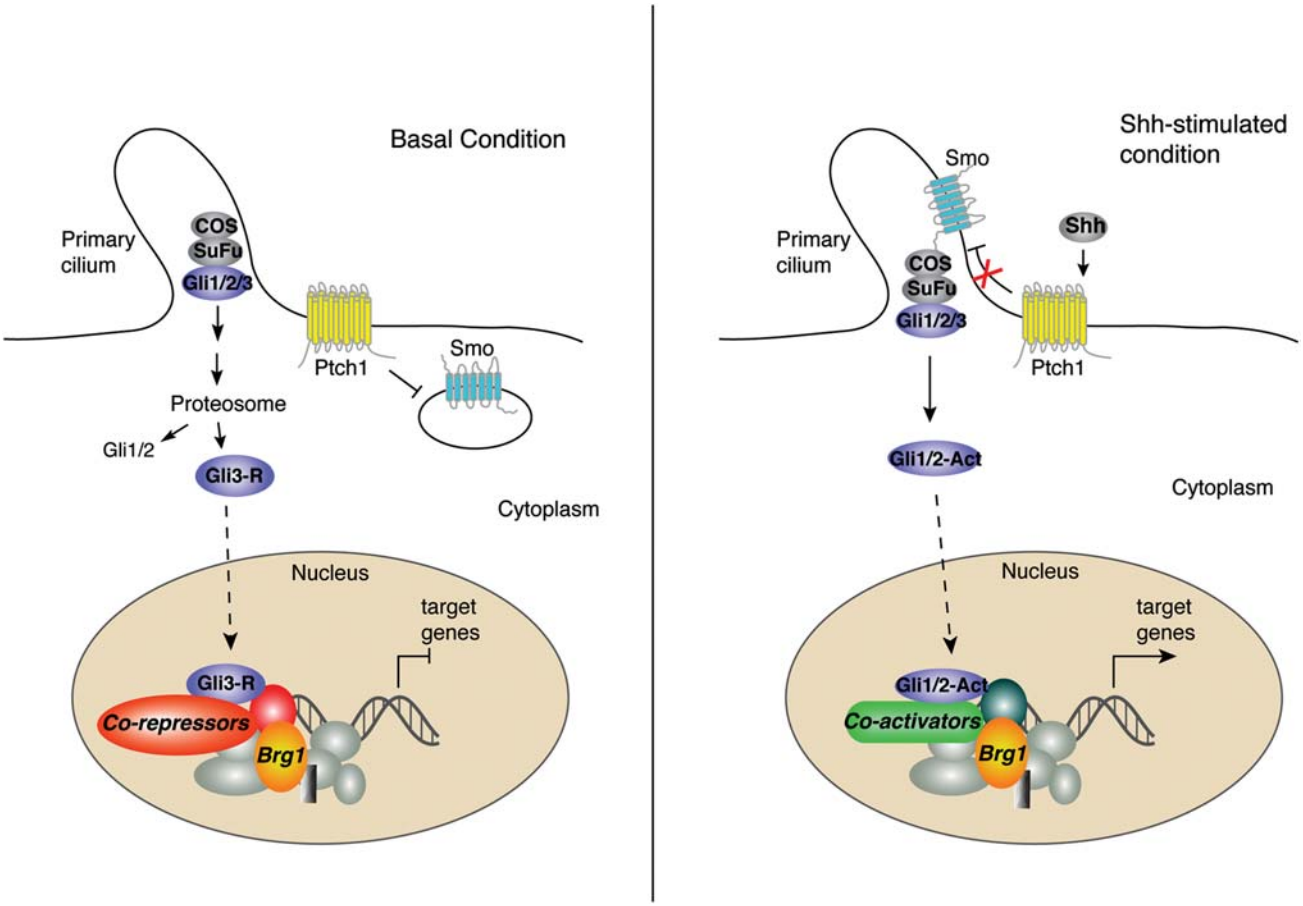

Figure 1 A possible model underlying dual functions of Brg1/BAF complexes in Shh signaling At basal condition, Ptch1 inhibits Smo, preventing its translocation to the primary cilium. Gli1/2 are mostly degraded, whereas Gli3 proteins are proteolyzed to form truncated Gli3R repressors. In the nucleus, Gli3R forms complexes with BAF and other corepressors to suppress target gene transcription. At Shh-stimulated condition, the binding of Shh to Ptch1 releases the inhibition of Smo. After translocating to the primary cilium, Smo activates Gli1/2 and prevents Gli3 processing. Activated Gli1/2 proteins interact with BAF complexes and other coactivators to mediate the Shh-induced transcription activation. The subunit compositions of BAF complexes in both conditions remain unclear and are represented by unmarked gray features. The red and green spheres represent potentially distinct BAF subunits that specifically interact with Gli3R or Gli1/2 and determine the repressor versus activator function of BAF complexes in regulating expressions of Shh target gene.

Gli family transcription factors [126–128]. Brg1 is required both for repression of the basal expression and for the activation of signal-induced expression of Shh target genes [35]. Thus, depending on local Shh concentration and the Shh signaling activity mode, Brg1 deletion may lead to increased or decreased Shh target gene expression. In developing telencephalons, dorsally expressed Gli3 actively represses Shh target gene expression, whereas ventrally expressed Shh functions to antagonize Gli3 repressor activity [129]. The balance between Shh and Gli3 repressor activity is required for proper specification of interneurons and oligodendrocyte progenitors [128,130,131]. *Brg1* deletion results in significant de-repression of Shh target genes in telencephalons, especially in the dorsal regions [35]. In contrast, during early post-natal cerebellar development, Shh produced by Purkinje neurons actively induces target gene expression in cerebellar granule neuron progenitors (CGNPs) and promotes CGNP proliferation [132,133]. *Brg1* deletion results in impaired CGNP responses to Shh, including changes in Shh-induced mitogenic target gene expression and in proliferation [35].

Our studies further indicate that Brg1/BAF complexes interact with different Gli factors and function independently of the ATPase activity of the complex [35]. Therefore, it is likely that BAF complexes play a structural role in regulating Shh target gene expression. A potential biochemical and functional protein network, consisting of Gli transcription factors, BAF complexes, and other chromatin-regulating cofactors, may work in concert to regulate target gene transcription and responses to Shh signals (**Fig. 1**). How BAF complexes switch function from repressor to activator upon Shh stimulation however remains unclear. The key may be different BAF subunit compositions in the activator versus repressor complexes. Further proteomic and functional analyses of individual BAF subunits in Shh signaling contexts may be required to solve the puzzle.

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Regulation of heart and muscle development by BAF complexes

Heart development involves the initial specification of cardiac progenitor cells from embryonic mesoderm and the later differentiation into the myocardium and the endocardium that form the basic layers of the heart. Cardiac progenitor expansion, differentiation, and heart morphogenesis require proper transcription regulation [134–136]. Several BAF subunits have been shown to be required during many stages of heart development, reflecting specific functions of different subunits at certain stages and locations.

Deletion of *Brg1* from endocardial cells early in development disrupts the interaction between endocardium and myocardium and leads to defective myocardial trabeculation, a key morphogenetic event during heart development [42]. Endocardial expression of *Brg1* is required for establishment of ventricle cardiac jelly through direct repression of the transcription of a metalloproteinase *ADAMTS1*. *Brg1* deletion causes elevated *ADAMTS1* expression and inhibition of metalloproteinase activity in cultured *Brg1* mutant embryos rescues the trabeculation phenotype. Thus, endocardial Brg1 plays a specific role in regulating the extracellular environment effective for myocardial morphogenesis.

In heart muscle development and pathogenesis, Brg1 is critical to cardiac growth, differentiation, and gene expression [41]. Accompanying cardiomyocyte development from the embryonic form to the adult one, the myosin heavy chain gene switches from expression of *β-MHC* to *α-MHC*. Stressed adult hypertrophic hearts re-activate expression of embryonic *β-MHC* and decrease *α-MHC* expression. Brg1 preserves fetal cardiac differentiation by activating *β-MHC* and repressing *α-MHC* expression. The level of Brg1 in adult cardiomyocytes is low, but increases in stressed adult hypertrophic hearts. Reducing Brg1 dosage in the adult heart effectively prevents stress-induced MHC misexpression and cardiac hypertrophy [41]. Thus, Brg1/BAF complexes have opposite effects on different MHC gene expression, and Brg1 levels are important for heart development and cardiomyopathy. Interestingly, reducing the Brg1 dosage may cause other heart defects since $Brg1^{+/-}$ mice display congenital heart defects such as dilated hearts and septum defects [43], indicating the importance of Brg1 dosage in regulating heart gene expression, heart development, and pathogenesis.

In addition to Brg1, several other BAF subunits have been shown to play critical and diverse functions during heart and muscle development. The PBAF-specific subunit BAF180 is necessary for normal heart chamber maturation and coronary development [77,78]. In these cases, PBAF may facilitate nuclear receptor-mediated transcription. In addition, BAF60c and BAF45c are both highly expressed in heart and muscle tissues. In zebrafish, mutations in either gene cause defects in heart and muscle development [84,137,138]. Mouse embryos derived from ES cells with BAF60c silenced by RNAi have defects in heart morphogenesis with impaired expansion of the anterior/secondary heartfield and abnormal cardiac and muscle differentiation [82]. The importance of BAF60c in heart development is also indicated by its ability to function together with transcription factors Gata4 and Tbx5 to initiate cardiac gene expression and reprogram mouse mesoderm to heart tissue [83].

During skeletal muscle development, BAF complexes and BAF60 also play important roles in activating muscle-specific genes and in myogenesis. During muscle differentiation, the p38 signaling pathway activates transcription of genes essential for muscle differentiation such as *myogenin* [139]. Activated p38 helps recruit BAF complexes to muscle-specific gene regulatory regions, possibly through phosphorylation of BAF60. It is not clear as to which BAF60 subunit is phosphorylated by p38 *in vivo*, and how the modification of BAF60 allows BAF complexes to target muscle genes.

Role of BAF complexes in immune system development and hematopoiesis

During thymocyte development, Brg1 and BAF complexes are required for the transitions of developing T cells to each developmental stage [36,37]. T cells develop through successive stages directed by external signals such as Wnt, pre-TCR, and TCR. BAF complexes likely function downstream of these signals to determine the transcription outcomes essential for thymocyte development [36]. Although it is not clear whether there are thymocyte-specific BAF complexes, different BAF subunits likely contribute to the interactions with specific transcription factors in different signaling pathways and with other transcription cofactors for diverse and precise transcription outcomes.

During thymic development two sub-lineages of T cells are produced with either CD4 or CD8 coreceptors. Using a dominant negative form of *BAF57*, as well as a *Brg1* mutation, it was shown that BAF complexes repress *CD4* and activate *CD8* expression [38]. At a later stage, BAF complexes are required for activation of the *CD4* gene. The repression of *CD4* gene requires the ATPase activity of BAF complexes, and it has been shown that BAF complexes remodel chromatin to facilitate the binding of transcription repressor Runx1 to a repressor site in the *CD4* gene [39]. In later stages, the activation of *CD4* by BAF complexes does not require the ATPase activity [104], indicating a structural role of BAF complexes in regulating CD4 expression and T-cell development.

During thymocyte maturation, it has been shown that expression levels of BAF subunits including Brg1 and BAF155/Srg3 are downregulated by TCR signaling. Constitutive expression of BAF155/Srg3 in developing

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thymocytes partially retained the BAF complex level and resulted in a change in the expression of genes important for the TCR-mediated intracellular signaling pathway. The disruption and impairment of normal thymocyte selections by constitutive expression of BAF155/Srg3 suggested that downregulation of the BAF complexes is required for proper thymocyte maturation [40].

During embryonic development, initial blood formation occurs in blood islands in the yolk sac, and later it occurs in fetal liver. Brg1 and other BAF subunits are required for regulation of β-globin expression and erythroid development in both tissues [44,45]. Deletion of the *Brg1* gene from developing erythrocytes impaired expression of α- and β-globin and primitive erythroid cell apoptosis [45]. A hypomorphic *Brg1* mutation led to defective definitive erythropoiesis. In *Brg1*-mutant fetal livers, erythroid progenitors develop normally until a block occurs at the basophilic-to-polychromatic erythroblast transition [44]. Interestingly, a *BAF250a* mutation in fetal liver stroma led to an increased fetal liver hematopoietic stem cell (HSC) population. The mutation enhanced the supportive environment, indicating a cell non-autonomous role of BAF complexes in fetal HSC proliferation and/or maintenance [140]. To date, no functional study of BAF complexes has been reported in bone marrow-derived HSC proliferation and differentiation, but it is clear that BAF complex is essential in myeloid cell fate determination [141]. It will be interesting to dissect the functions of BAF complexes in regulation of adult hematopoiesis.

In summary, during mammalian development, BAF subunits play diverse roles in regulation of many aspects of progenitor proliferation, differentiation, and tissue morphogenesis. Although BAF complexes regulate a large number of target genes at different developmental stages, specific subunits may contribute to the targeting specificity of the complexes in response to particular signaling pathways. The distinct phenotypes that result from deletion of individual BAF subunits may reflect the function of BAF complexes with specific subunit compositions and/or the function of the key target genes required at the time and location of development.

Function of BAF Complexes in Tumor Development

As a key epigenetic regulator, the BAF complex is involved in the formation of a large spectrum of cancer types. The activities of BAF complexes in tumor development appear to be tumor-type dependent and subunit dependent, as expected from the diverse functions of BAF complexes identified in different tissues during development.

Tumor suppressor functions of BAF subunits

Several BAF subunits have been shown to have tumor suppressor functions in different cancers. High-frequency mutations, deletions, or expression silencing have been reported for these subunits, indicating the potent functions of BAF complexes in repressing tumor formation. BAF47/SNF5 was the first BAF subunit to be considered a bona fide tumor suppressor protein [64]. Biallelic inactivation of *SNF5*, through deletion, mis-sense, nonsense, or frameshift mutations, is the cause of most malignant rhabdoid tumors (RTs), which are rare aggressive childhood cancers that affect brain, kidney, or other soft tissues [64–66]. In addition, *SNF5* mutations have been identified in several other cancers such as familial schwannomatosis and hepatoblastoma [67–69]. $SNF5^{-/-}$ mice die at an early embryonic stage, and 30% of *SNF5* heterozygotes develop tumors in brain and soft tissues resembling human RTs. The tumors also lose the wild-type *SNF5* allele [60–62]. Although SNF5 is essential for proliferation and survival of many wild-type cells, deletion of the *SNF5* gene in a mosaic pattern using an inverting conditional knockout strategy results in early-onset lymphomas and RTs with full penetrance [63], indicating a potent tumor suppressor function of *SNF5*. Interestingly, Brg1 is required for the tumor formation resulted from *SNF5* deletion, indicating that SNF5-negative BAF complexes may contain activities required for tumor formation [142].

As the core ATPase subunit of BAF complexes, *Brg1* has been reported to be silenced, deleted, or mutated in many cancer cell lines and/or primary tumors such as lung, pancreatic, breast, prostate, and colon cancers, and medulloblastoma and RTs [46,47,50,51,54,55,102]. Reintroducing Brg1 into the *Brg1*-negative SW13 cancer cell line induced differentiation and cell cycle arrest [102]. A small percent of *Brg1* heterozygous mice develop breast cancers, suggesting a tumor suppressor function of Brg1 [33,52]. In lung cancers, *Brg1* is among the most often mutated genes. *Brg1* mutation or silencing was identified in 20%–40% of non-small-cell lung carcinoma (NSCLC) cell lines [46,47]. *Brg1* mutations have also been identified in primary NSCLC tumors [48,49]. The high frequency of mutation rates far exceeds the possibility of random mutation in cancer cells. Deletion of *Brg1* from wild-type lung epithelial cells led to cell death; however, *Brg1* heterozygosity promoted tumor formation in urethane-induced lung cancer formation. Interestingly, deleting *Brg1* after urethane induction significantly increased lung cancer forming efficiency and tumor sizes [143], indicating that *Brg1* deletion may synergistically function with other mutations to promote lung cancer progression and maintenance. Indeed, *Brg1* mutations have been found to coexist with mutations in genes such as *KRAS*, *p53*, *LKB1*, and *CDKN2A* [46,47]. Despite the high frequency of *Brg1* mutations in NSCLCs,

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Brg1 mutation in small-cell lung carcinomas (SCLC) is rare [46]. Thus, the tumor suppressor function of Brg1 is cancer-type specific.

In addition to the frequent mutations of *Brg1* in cancers, its homolog *Brm* has also been found to be frequently silenced in lung and other cancers [47,102]. The absence of Brm from these cancers correlates with poor prognosis [47,57]. Although Brg1 and Brm share high similarity at the protein level, their relative expression levels in stem/progenitor cells and differentiated cells are different and they often perform distinct functions. *Brg1*-knockout mice die at an early embryonic stage [33], whereas *Brm*-knockout mice appear relatively normal except that they are ~15% larger than wild-type controls and have faster proliferation rate in certain tissues [56].

Recently, several other BAF subunits have been suggested to have tumor suppressor functions. BAF180, BAF200, and BAF250 are signature subunits of PBAF and BAF complexes, respectively. A large-scale mutation screen identified truncating mutations in BAF180/PBRM1 in 41% of clear cell renal carcinoma samples [79]. BAF180 are also mutated in breast cancer cell lines and tumors [80]. BAF200/ARID2 has been found mutated in all four major subtypes of hepatocellular carcinomas [76]. It has been reported that BAF250a/ARID1a was mutated in >50% of ovarian clear cell carcinomas, 30% of endometriosis-associated ovarian carcinomas, and 13% of transitional cell carcinoma of the bladder [72–74]. The high frequency of BAF180, BAF200, and BAF250a mutations indicates the importance of BAF and PBAF complexes in these tumors. In addition, mutations or altered expression of *BAF57* have been identified in various cancer cell lines and patient samples [51,70]. Deletions or decreased expression of the recently identified subunit Brd7 have also been reported in human breast tumors [81]. Although few mutations have been identified for BAF155 in human tumor samples, BAF155/Srg3 heterozygous mice have been shown to develop sarcoma, which was further enhanced by haploinsufficiency of p53 [144].

Thus, different BAF subunits have tumor suppressor functions in overlapping and distinct tumor subtypes, indicating common and specific contributions of the subunits to complex functions. Different subunits may target BAF complexes to target genes specifically important for development of certain cancer types. Alternatively, mutant BAF complexes may contribute directly to specific cancer formation.

Oncogenic function of BAF complexes

Although BAF subunits have tumor suppressor functions in many cancer types, evidence exists that in several cancer types the expression levels of Brg1/BAF subunits are increased, which promotes cancer progression. Brg1 levels are increased in primary melanomas and metastatic melanomas compared with dysplastic naevi. Knockdown of *Brg1* in melanoma cell lines results in significantly reduced cell proliferative ability [145]. In certain prostate cancers, Brg1 expression is significantly higher in malignant tissues than in benign compartments, and the expression levels correlate with tumor grade. Overexpression of exogenous Brg1 enhances cancer cell invasion in *in vitro* cell invasion assays [53]. Interestingly, *BAF155* expression is increased in prostate cancers, and higher levels of expression correlate with both tumor recurrence and de-differentiation [59]. In gastric carcinoma, an increased expression of Brg1 appears to be associated with the development and progression of the cancer [146]. In human colorectal carcinoma (CRC) samples, expression of Brg1, but not Brm, is frequently elevated. Knockdown of *Brg1* suppressed cell proliferation in a CRC cell line. In CRC cells, Brg1 may mediate repression of phosphatase and tensin homolog (PTEN) expression and subsequent cyclin D1 activation [147].

Possible mechanisms underlying diverse BAF subunit functions in cancers

Mutations or alterations in levels of expression of BAF subunits are associated with development of many cancer types. Although the molecular functions of BAF subunits during normal development and during cancer progression have been extensively studied, it is difficult to find a common theme for the mechanisms underlying the tumor suppressor or oncogenic activities. BAF complexes regulate many target genes and multiple signaling pathways important for cell proliferation and differentiation. The final transcription outcomes of BAF target genes and their effects on cells are highly dependent on tissue type and cell context. Thus, it is likely that the responses to certain BAF-regulated signaling pathways by specific tumors, the different requirements for disrupted tumor suppressor pathways, and the different BAF complex compositions and activities together determine the diverse molecular functions of BAF complexes in tumor formation and progression.

The first tumor suppressor activity of Brg1/BAF complexes discovered resulted from complex formation with the tumor suppressor RB to repress cell-cycle-related genes and induce cell cycle arrest [102,148]. The effects on tumorigenesis by inactivating both *SNF5* and *RB* in mouse tissues are not significantly higher than deleting SNF5 alone, indicating the overlapping functions between BAF complexes and RB [149]. However, in certain cancers, such as SCLCs, which are characterized by universal loss of RB, few mutations have been found in *Brg1* or other BAF subunits despite the high-frequency mutations in other lung cancer types such as NSCLCs [149]. The lack of BAF mutations in SCLCs indicates that Brg1/BAF

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complexes may regulate additional pathways essential for SCLC formation. BAF complexes are now known to interact with several other tumor suppressors such as p53 and BRCA1 [94,150]. Several BAF subunits such as Brg1, Brd7, BAF60a, and BAF53a have been shown to interact with p53 and facilitate p53-mediated transcription activation of tumor repressors such as p21 [81,94,95,151,152]. However, in many cancers, BAF mutations coexist with p53 mutations [46,47], suggesting that BAF complexes may regulate other tumor suppressor pathways that synergistically function with the p53 pathway.

Besides cooperating with other tumor suppressors, BAF complexes can also regulate tumor formation by modulating oncoprotein activities or oncogene expression. For example, BAF subunits are able to interact with c-Myc and regulate Myc-mediated transcription activation [153]. In addition, BAF complexes can also regulate *c-Myc* expression. Interestingly, with different BAF250 subunits incorporated, BAF complexes either repress or activate *c-Myc* expression [154,155]. PcG proteins such as EZH2 display oncogenic activities, and their expression is often upregulated in cancers [156,157]. As mentioned earlier, BAF complexes can antagonize PcG function in ES cells by competing for binding sites [114]. In addition, BAF complexes also repress PcG gene expression. It has been shown that in *SNF5*-mutation-induced tumors, PcG expression is significantly upregulated. Inactivation of Ezh2 blocks tumor formation driven by *SNF5* loss [158]. Thus, the regulation of oncogene expression and/or activities contributes to BAF tumor-suppressive and oncogenic activities under specific contexts.

Many signaling pathways are important for both normal development and cancers. A better understanding of the function of BAF complexes in developmentally important signaling pathways may shed light on the mechanisms underlying their tumor-suppressive and oncogenic activities. BAF complexes have been shown to function in multiple signaling pathways such as those mediated by Shh, Notch, Wnt, JAK/STAT, and nuclear hormone receptors [27,35,110,114,159–162]. The specific functions of these pathways in different types of cancers indicate that BAF complexes sometimes suppress and sometimes promote tumor formation depending on context. For example, the diverse functions of BAF complexes in regulation of Shh signaling may result in opposite effects of BAF complexes in different cancers.

Elevated Shh signaling is linked to various cancers. Mutations resulting in an overactive Shh pathway are the leading cause of the childhood brain tumor medulloblastoma [163]. These Shh subtypes of medulloblastoma and several other cancers, such as basal cell carcinoma, require active Shh target genes for initiation and maintenance. In many other cancer types, elevation of Shh target genes does not initiate tumors, but is associated with tumor maintenance [163]. Deletion of *Brg1* and BAF subunits has a tissue-dependent effect on Shh target gene expression [35]. Thus, BAF complexes may promote or suppress tumor formation depending on the requirements of the specific cancer for Shh-mediated gene expression. BAF complexes repress the basal expression of Shh target genes [35,159]. RTs that result from *SNF5* loss have elevated levels of Shh target genes. Knockdown of *Gli1* reduces tumor proliferation and allograft tumor formation rate [159]. Thus, repressing Shh target gene expression may contribute to the tumor suppressor activity of SNF5. On the other hand, in the cancers that require activated Shh signaling, such as Shh-type medulloblastoma, BAF complexes may be required for tumor initiation and/or progression since BAF complexes are required for Shh-induced target gene activation in CGNPs [35]. In a mutation screen of 88 medulloblastoma samples, four mutations were identified in BAF subunits (three in *Brg1* and one in *BAF250*a). However, none of the mutations coexist with *Ptch1* mutations (typical of Shh-type medulloblastoma) despite the high occurrence of *Ptch1* mutations (25%) [55]. Thus, the dual role of BAF complexes in Shh signaling may contribute to the diverse function of BAF complexes in cancer formation.

Mouse models to study BAF function in cancer development

Mouse models are essential tools for analysis of gene functions in cancer development. Although alterations of BAF subunits have been found in many cancer types, most studies of their molecular functions in cancers were performed in cancer cell lines. Cancer cell lines are often selected for growth and survival in cultured conditions and lack stromal tissues; therefore, they may not truly be representative of cancer development *in vivo*. In addition, the genetic backgrounds of cancer cell lines are ambiguous and BAF subunits may harbor unidentified mutations or have altered levels of expression that facilitate cell growth. Thus, the results obtained from cell line studies must be verified using *in vivo* models. Unfortunately, there are few mouse models suitable for cancer studies of BAF subunits. Although quite a few knockouts and conditional knockouts of different BAF subunits have been generated, the essential functions of BAF subunits during development and in normal cell proliferation/survival hamper the discovery of their cancer-related functions. Although tumors develop in *Brg1* and *SNF5* heterozygous mice, the percentages are low and the tumors are late-onset [52,60,61]. To date, except for the inverted *SNF5* conditional knockout mice [63], most conditional knockouts of BAF subunits are not suitable for cancer studies as deletion of BAF subunits often leads to cell cycle arrest and apoptosis.

However, BAF complexes are not likely essential for cell proliferation or survival *per se* since many cancer cells lack certain BAF subunits. Thus, it is possible that deletion

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of BAF subunits triggers the activation of other cell surveillance pathways and causes cell cycle arrest and apoptosis indirectly, a phenomenon similar to what happens when oncogenes are overexpressed in wild-type cells. Indeed, p53 is activated after *Brg1* or *SNF5* loss [149,164], and deletion of p53 in *SNF5*$^{-/-}$ cells significantly shortens the time to cancer development [149]. Thus, new strategies need to be developed to generate mouse models for the study of BAF subunits in cancer development. Once the cell protection pathways activated by BAF deletion are identified, deletion of BAF subunits together with deletion of the synergistic factors will reveal the tumor suppressor activities of BAF subunits. Another option is to use a strategy similar to that employed in the *SNF5* mouse model, which generates deletions in a mosaic pattern to maintain tissue integrity and mouse survival [63].

Conclusions and Future Perspectives

Mammalian SWI/SNF-like BAF complexes play various roles during development and adult homeostasis and in cancer progression. Several factors contribute to the diverse functions of BAF complexes under different contexts. First, BAF complexes use multiple mechanisms to regulate transcription outcomes. The ATPase-dependent chromatin-remodeling activities directly regulate histone–DNA interactions and change the accessibility of regions of DNA to transcription factors. In an ATP-independent manner, BAF complexes recruit other chromatin regulating factors that control gene expression to DNA regulatory regions. Second, the combinatorial assembly of BAF subunits generates large numbers of BAF complexes with distinct subunit compositions. As different subunits interact with specific sets of transcription factors and cofactors, this provides a mechanism to increase specificities and diversities of BAF target genes and chromatin-modulating activities. Third, the activities of the many BAF target genes determine the diverse roles of BAF complexes in normal development and cancers. In a specific cell type during certain developmental stages, BAF-regulated transcription programs determine the specific cell states and physiological conditions. BAF complexes may promote or repress tumor formation depending on the effects of key target genes required for the development of specific types of cancers.

To systematically understand the biochemical, molecular, cellular, and developmental roles of BAF complexes, new tools, techniques, and approaches are needed. Firstly, *in vitro* and *in vivo* assays that accurately reflect BAF complex functions are needed to understand the structure–function relationship between BAF subunits and BAF complexes in transcriptional regulation. Further, the specific BAF subunit compositions and the identities of target genes must be elucidated in order to determine the *in vivo* functions of BAF complexes during development and cancer formation. With recent advancements of sensitivity and accuracy of mass spectrometry technology, it is now possible to identify BAF complex subunit compositions and specific interacting proteins from a small amount of cells isolated from a specific developmental stage; these data will provide a framework for determining specific functions of BAF complexes in different tissues. In addition, the application of the recently developed methods of genome-wide gene expression and DNA-binding analysis to BAF complexes, combined with the comparison with other chromatin modifications, will provide a comprehensive understanding of the epigenetic states of BAF target genes in different cell types. Finally, new mouse models must be developed to examine the *in vivo* functions of BAF subunits in cancer development. A systematic understanding of diverse functions of BAF complexes, the relationship between BAF complexes and other epigenetic regulating factors, and the key target genes or pathways will provide opportunities to develop novel therapeutic strategies to treat BAF-related diseases and cancers.

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