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Review Article

The SWI/SNF ATP-dependent chromatin remodeling complex in cell lineage priming and early development

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ATP dependent chromatin remodelers have pivotal roles in transcription, DNA replication and repair, and maintaining genome integrity. SWI/SNF remodelers were first discovered in yeast genetic screens for factors involved in mating type switching or for using alternative energy sources therefore termed SWI/SNF complex (short for SWItch/Sucrose NonFermentable). The SWI/SNF complexes utilize energy from ATP hydrolysis to disrupt histone-DNA interactions and shift, eject, or reposition nucleosomes making the underlying DNA more accessible to specific transcription factors and other regulatory proteins. In development, SWI/SNF orchestrates the precise activation and repression of genes at different stages, safe guards the formation of specific cell lineages and tissues. Dysregulation of SWI/SNF have been implicated in diseases such as cancer, where they can drive uncontrolled cell proliferation and tumor metastasis. Additionally, SWI/SNF defects are associated with neurodevelopmental disorders, leading to disruption of neural development and function. This review offers insights into recent developments regarding the roles of the SWI/SNF complex in pluripotency and cell lineage primining and the approaches that have helped delineate its importance. Understanding these molecular mechanisms is crucial for unraveling the intricate processes governing embryonic stem cell biology and developmental transitions and may potentially apply to human diseases linked to mutations in the SWI/SNF complex.

The development of a multicellular organism initiates with a single-celled zygote, which undergoes rapid cell division, giving rise to the formation of the inner cell mass (ICM). Embryonic stem cells (ESCs) isolated from this early stage are referred to as being in a naïve pluripotent state [1]. These cells possess the remarkable ability for self-renewal and can differentiate into various cell types in response to appropriate stimuli. The naïve pluripotent state is characterized by the expression of specific transcription factors (TFs), a hypomethylated genome, and is prominent during the pre-implantation stage of mouse development [2–4]. Following implantation, ESCs experience significant epigenetic changes leading to a global shift in gene expression. This transformation is accompanied by increased DNA methylation, a loss of self-renewal capacity, and a transition towards epithelialization [2,5,6]. This altered cellular state is recognized as the primed or epiblast cell state[1]. During this stage, cells express lineage-specific TFs and become primed to differentiate into the three germ layers, subsequently giving rise to various tissues and organs [7–9].

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Cell models for studying pluripotency and early mammalian development

The pluripotent state is highly transient during embryonic development, lasting only for a short period *in vivo*; however, cells representative of the pluripotent state can be captured and stably

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maintained *in vitro*. Mammalian ESCs were first cultured ex vivo from cells derived from the ICM of the blastocyst with the capacity to differentiate into any cell type. At first it was thought there was a single pluripotent state, but it now appears there is a continuum of different pluripotent states [10]. Early on the human and mouse ESCs were found to behave differently with mouse ESCs being more representative of cells in the pre-implantation stage and human ESCs representative of epiblast cells from post-implantation [11]. Later studies showed that human ESCs could be made that were more like mouse ESCs and these are collectively referred to as naïve stem cells [12]. Similarly, mouse ESCs can be cultured to resemble human ESCs and are referred to as EpiSC (epiblast stem cells) or primed stem cells [13,14]. For the purpose of this review we will refer to EpiSC simply as primed stem cells. The naïve and primed stem cells are representative of initial and final stages of pluripotency. Naïve and primed cell types resemble their counterparts in the embryo and featured by several distinct epigenetic, transcriptional, metabolic, and cell signaling changes (see Table 1). Although, these two cell types have limited representatives of embryogenesis, nonetheless proven to be invaluable in studies of early mammalian development.

There is a third class of stem cells representative of an intermediate state in pluripotency referred to as formative stem cells that have germline induction, a feature missing in both the naïve and primed stages. One type of cells with features of this type are called epiblast-like cells, which resemble cells in the pre-implantation epiblast that are maintained with bFGF and activin but unfortunately are heterogeneous [90,91]. On going efforts have uncovered better culture conditions for isolation of formative pluripotent stem cells whose transcription profile resembles that seen in pre-gastrulation formative epiblast and have super-bivalency at a large number of developmental genes [91–93]. The discovery of formative pluripotent cells indicates that the pluripotent state needs to be disassembled to some extent before lineage priming can be initiated.

Metabolism in the different stages of pluripotency

Stem cells, owing to their rapid division, experience a heightened demand for metabolic precursors essential for DNA replication. Simultaneously, these cells necessitate substantial ATP hydrolysis, a process that significantly influences both the epigenetic and transcriptional landscape. There are major differences in the metabolic states of naïve and primed stem cells (Table 1) with naïve cells using both glycolysis and oxidative phosphorylation for energy and primed cells primarily glycolysis [10]. Another difference is fatty acid oxidation being required for naïve stem cell maintenance and not for the primed stage [60,64,94]. The intermediate formative stage between the naïve and primed stages has a strong reduction in mitochondrial respiration and increased levels of lipid metabolic enzymes compared with the naïve and primed stage [68,93,95].

Some of the metabolic and signaling proteins involved in the transition from naïve to primed states are identified by tracking changes in nascent RNA transcription using techniques like PRO-seq [61]. These proteins are involved in (1) glycolysis, (2) oxidative phosphorylation, (3) lipid metabolism, (4) glutamine transport, (5) regulation of adenine nucleotide levels and (6) G-protein coupled signaling (Figure 1 and Table 1). The Sirt2, Tigar (fructose-2,6-bisphosphatase) and G6pc3 (glucose 6 phosphotase 3) genes are expressed primarily in mouse naïve ESCs and facilitate in down-regulating glycolysis. Sirt2 is an NAD-dependent deacetylase that deacetylates several glycolytic enzymes (GAPDH, PGK1, ENO1, PKM and ALDOA) and thereby inactivates them while also activating oxidative phosphorylation [96,97]. The genes encoding several mitochondrial proteins involved in oxidative phosphorylation and those in lipid metabolism are repressed in the primed stage, consistent with the switch to primarily glycolysis in the primed stage and the importance of lipids in pluripotency (see Figure 1). There is an increased need for glutamine due to rapid proliferation and is likely the reason for the increased expression of *Asct2* (alanine, serine, cysteine transporter 2) in the naïve compared with primed stage. Asct2 is a neutral amino acid transporter, whose preferred substrate is the conditionally essential glutamine [98]. Next, the *Ak9* gene encoding nucleoside-diphosphate kinase is expressed higher in naïve than primed cells and regulates the level of adenine nucleotides in line with the higher demand for ATP in the naïve stage [99]. The G-protein coupled signaling pathway is important for ESC proliferation and its physical properties and expression of several genes encoding various isoforms of the guanine nucleotide binding protein/receptor are more highly expressed in naïve than primed cells[100,101].

These metabolic and signaling changes that occur between the naïve and primed stages are conserved across mouse and human as well as in their pre and post implantation embryonic states reflect the reconfiguring of a pluripotent state in the transition to cell lineage priming and cell fate determination by removing basic inherent properties of pluripotency (Table 1).

Table 1. Comparision of various key features in during naïve to primed transition in mouse and human ESCs and early embryonic stages.

	Naive pluripotent state				Primed pluripotent state				
	Mouse		Human		Mouse		Human		
Key features	***In vitro***	***In vivo***	***In vitro***	***In vivo***	***In vitro***	***In vivo***	***In vitro***	***In vivo***	**References**
Epigenetic regulation									
Global DNA methylation	Hypo	Hypo	Hypo	Hypo	Hyper	Hyper	Hyper	Hyper	[15–20]
X chromosome inactivation in female cells	No	No	No	No	Yes	Yes	Yes	Yes	[21–24]
H3K27me3 on developmental genes	Low	Low	Low	Low	High	High	High	High	[25–29]
OCT4 enhancer switching	Distal	Distal	Distal	Distal	Proximal	Proximal	Proximal		[30–33]
Chromatin accessibility	High		High	High	Low		Low		[34–37]
Transcriptional regulation									
Priming markers (ZIC2, OTX2)	Low	Low	Low	Low	High	High	High	High	[2,26,30,38,39]
Pluripotency markers (KLFs, NANOG,)	High	High	High	High	Low	Low	Low	Low	[2,9,38,40–44]
ESRRβ	High	High	High	low	Low	Low	Low	Low	[43,45–48]
Cadherin	E- type	E- type	E- type	E-type	N- type	N- type	E-type		[26,49–52]
c-KIT expression	Yes	Yes	Yes	Yes	No	No	Yes	No	[53–57]
CD24/MHC class 1	Low	Low	Low	Low	High	High	High	High	[41,58,59]
Metabolism									
Oxidative phosphorylation	High	High	High		Low	Low	Low		[60–63]
Glycolysis	Low	Low	Low	Low	High	High	High	High	[61,64–67]
Lipid metabolism	High	High	High		Low	Low	Low		[61,68–70]
Polyamine metabolic pathway	High	High	High		Low	Low	Low		[71–73]
Threonine metabolism	High	High	High		Low	Low	Low		[73–75]
SAM levels	High	High	High		Low	Low	Low		[76,77]
α-keto glutarate	High	High			Low	Low			[78]
Amino acid/ATP	High	High	High		Low	Low	Low		[61,73]
Cell signaling and cell cycle									
MEK–ERK dependence	No	No	No		Yes	Yes	Yes		[2,26,79,80]
Wnt dependence	Yes	Yes	Yes	Yes	No	No	No		[2,81–83]
G-protein coupled signaling	High		High		Low		Low		[61,84,85]
Cell cycle	High		High		Low		Low		[61,86]
CDK2 dependency	Yes		Yes	No	No		No		[87,88]
Telomere length maintenance	Yes				No				[89]
DNA repair capacity	High				Low				[89]

Molecular and epigenetic characteristics of the naïve and primed stages

Some of the characteristics that distinguish naïve from primed stem cells are the lack of female X-chromosome inactivation, the ability of self-renewal when MEK signaling is inhibited and to generate chimeric embryos [10]. Wnt/β-catenin signaling is needed for naïve stem cell self-renewal and inhibits the transition into primed stem cells [102,103]. Mouse naive ESCs divide unusually rapidly with a particular short G1-phase and ∼50–70% of the cell cycle is in the S-phase [104]. The G1 phase is shorter due to the unregulated or constitutive expression of the CDK2 (cyclin dependent kinase 2). The G1 phase becomes longer as cells begin to differentiate and synthesis of CDK2 become more tightly regulated and expressed at lower levels.

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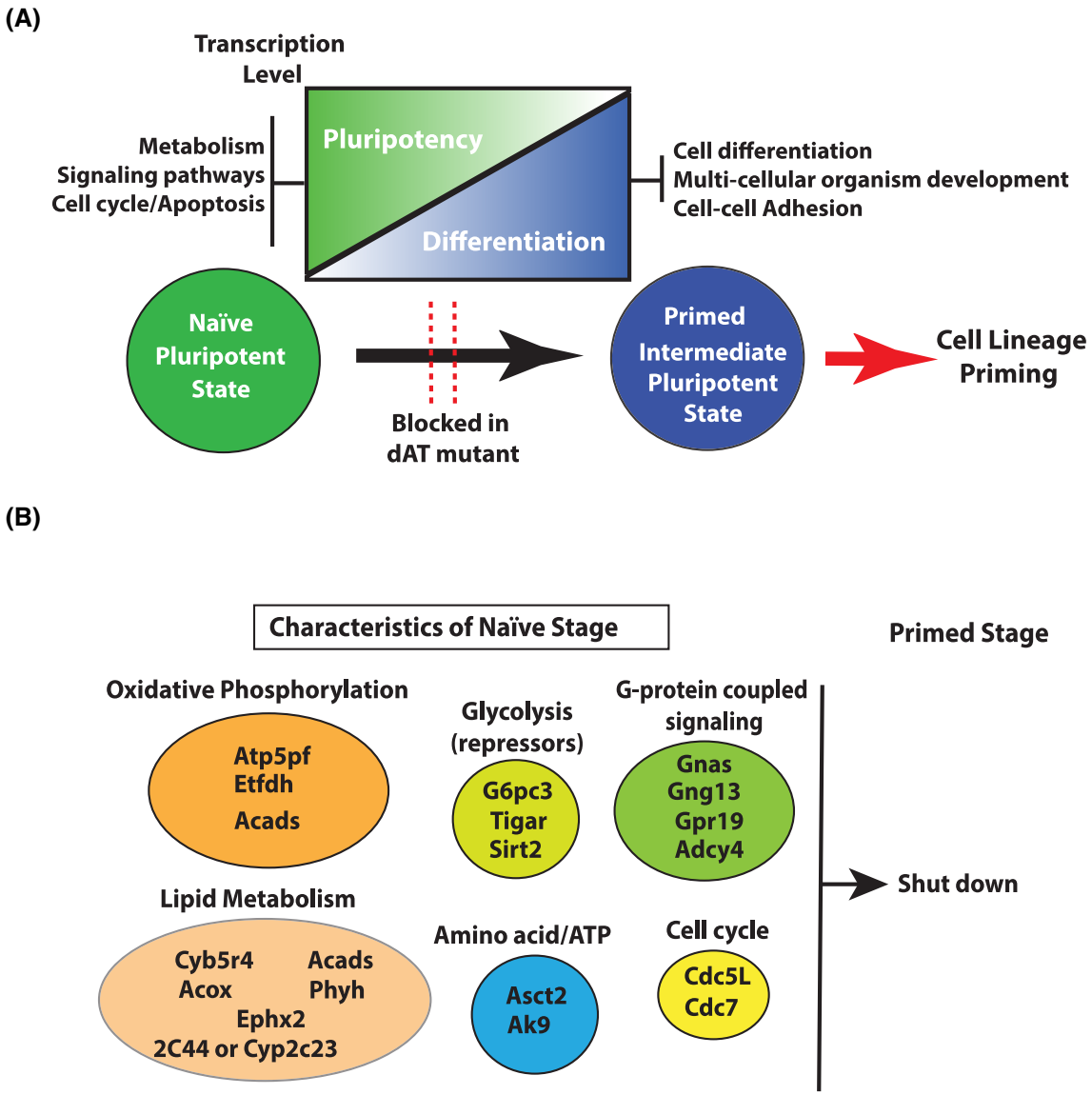

Figure 1. Key changes in major signaling pathways during naïve to primed stage transition.

(**A**) Key changes in pathways in naïve to primed transition stage. Deletion/mutation of Brg1 AT-hook blocks these signaling pathways and affects cell lineage priming. (**B**) List of active metabolic genes/pathways in naïve pluripotent stage which are shoutdown in the primed stage. (Atp5pf = ATP synthase-coupling factor 6; Etfdh = electron transfer flavoprotein-ubiquinone oxidoreductase; Acads = short-chain specific acyl-CoA dehydrogenase; G6pc3 = glucose-6-phosphatase 3; Tigar = fructose-2,6-bisphosphatase; Sirt2 = NAD-dependent protein deacetylase sirtuin-2; Gnas = guanine nucleotide-binding protein G(s) subunit α isoform; Gng13 = guanine nucleotide-binding protein G(l)/G(S)/G(O) subunit γ-13; Gpr19 = G-protein coupled receptor 19; Adcy4 = adenylate cyclase type 4; Cyb5r4 = cytochrome b5 reductase 4; 2C44 or Cyp2c23 = cytochrome P450; Acox = peroxisomal acyl-coenzyme A oxidase 1; Ephx2 = bifunctional epoxide hydrolase 2; Phyh = phytanoyl-CoA dioxygenase, peroxisomal; Cdc5L = cell division cycle 5-like protein; Cdc7 = cell division cycle 7-related protein kinase; Asct2 = alanine, serine, cysteine transporter; Ak9 = protein adenylate kinase 9).

The metabolic changes described earlier are often tied to changes in the epigenetic state of naïve and primed stages. Typically, during the transition from the naïve to primed stage, genomic DNA undergoes a shift from hypomethylation to methylation, with trimethylation occurring at histone H3 lysine 27 in lineage regulatory genes during the primed stage [25,26,105]. These changes in DNA methylation parallel the

observations in early embryogenesis, where DNA experiences global demethylation followed by remethylation. However, both pre- and post-implantation mouse epiblast cells maintain a hypomethylated state [106]. In the naïve stage, DNA demethylation at pluripotency genes is orchestrated by PRDM14 (PR domain containing 14), recruiting TET1/TET2 and repressing de novo methyltransferase [107]. Overexpression of PRDM14 in the primed stage induces a conversion to the naïve stage, facilitating OCT3/4 recruitment to the enhancers of naïve pluripotency genes [108]. Throughout this conversion, PRDM14 also represses primed stage-specific genes through PRC2 complex recruitment and accompanying trimethylation of lysine 27 of H3 (H3K27me3) [109]. In murine pre-implantation embryos, H3K27me3 and H3K4me3 possess distinct dynamics where H3K4me3, especially on promoter regions, occurs much more rapidly than that of H3K27me3 following fertilization, which is consistent with the major wave of zygotic genome activation at the two-cell stage [27]. Chromatin in the naïve stage adopts a more open state, enhancing transcription compared with the more closed state observed in the primed stage, akin to the patterns observed in pre- and post-implantation embryos[110].

The transition from naïve to primed stages involves substantial enhancer or cis-regulatory element switching. This is evident through changes in the localization of monomethylated lysine 4 of histone H3 (H3K4me1) and acetylated lysine 27 of histone H3 (H3K27ac), as well as the binding of TFs. Enhancers are either decommissioned or activated in a stage-specific manner [30,61,111]. Corresponding alterations in enhancer-promoter interactions are observed between the naïve and primed stages in human and mouse ESCs [112,113]. During this transition, enhancer-promoter interactions for the same gene are modified, as exemplified by OCT4. The OCT4 gene possesses distal and proximal enhancers, with the distal enhancer primarily responsible for activation in the naïve stage and the proximal enhancer assuming dominance in the primed stage [30,31]. These enhancers appear to be regulated by repressive histone modifications and DNA methylation in a stage-specific manner[32]. While pluripotency TFs remain crucial in both stages, they operate in different contexts. Oct4 TF, for instance, is essential for both pluripotency maintenance and exit, with its genomic localization undergoing global alterations in the transition from naïve to primed stages. The binding of Oct4 and Sox2, inferred by ATAC-seq, can be categorized into three classes: naïve or primed stage-specific and those present in both stages [30,61].

Despite the extensive work in this area, there is still much that is unknown about how changes in the transition to cell lineage priming are regulated and particularly the role of ATP-dependent chromatin remodeling in this process.

Diversity of mammalian SWI/SNF complexes

A critical player in cell fate determination are the family of SWI/SNF ATP-dependent remodelers which are often referred to as BAF (BRG1 or BRM associated factors) complexes. At the heart of the SWI/SNF is an ATP-dependent DNA translocase that binds and translocates along the DNA wrapped around the nucleosomes, the most basic component of chromatin. DNA translocation along nucleosomal DNA can have one of three basic outcomes. The first is moving the nucleosome to different positions on DNA with the ability to create regions of free DNA devoid of bound histone [114]. Instead of merely rearranging nucleosome positions, SWI/SNF also has the capacity of completely displacing parts of nucleosome (a.k.a. H2A-H2B dimers) or entirely evicting nucleosomes from DNA [115,116]. A third property of ATP-dependent chromatin remodelers not observed with SWI/SNF complexes are the ability to change nucleosome composition by exchanging dimers with different histone isoforms (a.k.a. H2A-H2B for H2A.Z-H2B) [117].

There are several ways in which SWI/SNF is recruited to the correct target sites involving factors that together with SWI/SNF reciprocally facilitate each other's binding. DNA sequence-specific TFs like hormone receptors or pioneer TFs have been shown to recruit SWI/SNF [118–120]. The other mode of stabilizing SWI/SNF binding to genomic sites is through its interactions with post-translationally modified histones [121–123]. The 2-megadalton SWI/SNF complex has a wide arrange of various histone reader domains including bromodomain in Brg1, plant homology domain in BAF45 and chromodomain in BAF155 and BAF170, that can bind to variety of covalently modified residues residing in nucleosomes and increase the residence time of SWI/SNF on chromatin[124,125]. Transcriptional co-activators like p300/CBP, a histone acetyltransferase, and MLL3/4, a histone methyltransferase, have also been found to promote SWI/SNF binding to chromatin independent of their associated modification that is likely mediated through direct protein-protein interactions between the complexes [126–128]. There are likely other factors involved in SWI/SNF recruitment that have not yet been

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uncovered. In mammals, SWI/SNF is recruited to both promoter and enhancer regions to activate transcription and is highly enriched at super-enhancers, cis-regulatory regions known to determine cell type specificity [129].

Mammalian SWI/SNF has two catalytic subunits called BRG1 (SMARCA4) and BRM (SMARCA2) that contain the DNA-dependent ATPase domain and are assembled mutually exclusive of each other in distinct SWI/SNF complexes. There are 9–11 other subunits that assemble with the catalytic subunit to form a complete complex. These accessory subunits are encoded by 27 different genes and accounts for the diverse complex composition of SWI/SNF that varies in a cell-type specific manner [130]. There are three basic families of mammalian SWI/SNF called cBAF, PBAF and ncBAF/GBAF that differ by the composition of the accessory subunits and contain BRG1 or BRM. The PBAF (Polybromo-associated BAF complex) is distinguished from the cBAF (canonical BAF complex) by the incorporation of BAF180 (PBRM1) and BAF200 (ARID2) subunits and in cBAF BAF200 is replaced by BAF250A/B (ARID1A/B). Furthermore, PBAF lacks SS18 but includes the PBAF-specific subunits BAF45A and BRD7 [131,132]. The ncBAF (for non-canonical BAF complex) or GBAF is characterized by the incorporation of BRD9 and GLTSCR1/1L and lacks the cBAF subunits BAF47 (SMARCB1), BAF57(SMARCE1), and BAF250 and the PBAF-specific subunits BAF200, BAF180, BAF45A (PHF10) and BRD7 [133–135].

The heterogeneity of these BAF complexes presumably leads to functional differences important in various developmental stages including pluripotency and cell lineage priming. In ESCs there are only three type of SWI/SNF complexes, esBAF — the embryonic version of the cBAF complex, GBAF and PBAF[136–138]. Highly abundant esBAF and GBAF complexes have primarily the Brg1 catalytic subunit as Brm is minimally expressed in naïve and primed stages of ESCs [136,139]. The embryonic stem (es)BAF complex is required for self-renewal and maintenance of ESCs, but its role in cell lineage priming and in the transition from naïve to primed ESCs has been unknown until a recent study[61]. The esBAF is essential for gene expression of many of the pluripotency TFs, as shown by esBAF binding to the key regulatory regions of the genes encoding for these factors and their diminished expression when Brg1 is deleted [139,140]. Mouse esBAF is distinguished by containing BAF250a not BAF250b, BAF60a/b instead of 60c and a homodimer of BAF155 (SMARCC1) instead of BAF155 and BAF170 heterodimer [131,139]. In human ESCs, there is a heterodimer of BAF170 and BAF155 which is important in pluripotency maintenance [141].

BRG1 and esBAF role in pluripotency

The functional significance of Brg1 and the esBAF complex in mouse embryonic development is underscored by knockout of Brg1 causing lethality at the pre-implantation stage [142–144]. The embryonic BAF complex (esBAF) works cooperatively with the core pluripotency TFs (Oct4, Sox2, Nanog) [138,145]. Initially, Brg1 was known to bind promoters of pluripotency-related genes to regulate self-renewal [143]. Recently Oct4 has been shown to recruit Brg1 to cis-regulatory elements of pluripotency genes including Oct4 and is a self re-enforcing system of gene regulation [119]. While Brg1 is a linchpin component, other BAF complex subunits also wield significant influence in pluripotency preservation and differentiation.

Brm, although non-essential in mice, exhibits context-dependent effects [146,147]. Deleting Brm in ESCs does not compromise pluripotency but alters differentiation trajectory from precardiac mesoderm to non-mesodermal neural precursor lineage by preventing *de novo* accessibility at primed cardiac enhancers and activating neurogenic TF POU3F1 during cardiac differentiation [148]. BAF250A and BAF250B play unique roles in regulating pluripotency and lineage decisions [137,149]. Deleting BAF250A in ESCs results in reduced differentiation of cardiac mesodermal progenitors by leaving neuroectoderm lineage formation unaltered, illustrating its role in modulating lineage determinations by regulating OCT4 and β catenin recruitment to the lineage specific genes [150]. In addition to the well-delineated esBAF complex, the recently identified ncBAF assumes a crucial role in controlling the ESC transcriptome. Inhibiting the ncBAF subunit Brd9 triggers ESCs to adopt a morphology reminiscent of primed or epiblast ESCs, reduces colony-forming capacity, and down-regulates key pluripotency genes like Nanog and Klf4, underscoring Brd9's pivotal role in preserving the naive pluripotent state of ESCs [136]. Another esBAF component, Dpf2, influences meso-endodermal lineage differentiation by binding to and activating Tbx3 distal enhancer and modulating key factors like Tbx3 and Nanog, crucial for ESC self-renewal and differentiation [151–155]. BAF47, also part of the complex, controls ESC differentiation through Oct4 regulation, impacting the balance between pluripotency and differentiation [156]. Several other BAF subunits also influence pluripotency gene expression, highlighting the intricate regulatory network governing pluripotency and differentiation [138,145,149].

Beyond pluripotency maintenance, Brg1's functions extend to trophectoderm development, where it represses Nanog and Oct4 through an HDAC1 and Cdx2 mediated mechanism [157,158]. Moreover, significance of the BAF complex extends to the generation of induced pluripotent stem cells from differentiated cells. Brg1 is indispensable for reprogramming, and its overexpression bolsters reprogramming efficiency, while down-regulating Brm facilitates reprogramming [159–161]. Additionally, the inability of Brm or BAF170 to rescue the loss of Brg1 or BAF155, respectively, emphasizes the specificity and indispensable role of these subunits within the complex [138].

The connection between Brg1 and its AT-hook in early development

The AT-hook motif, originally discovered in the High Mobility Group AT-hook 1 (HMGA1) protein, has emerged as a critical and conserved DNA-binding motif found in numerous chromatin-associated proteins, which at its core has the tripeptide R-G-R flanked by proline residues [162]. Crystallography and nuclear magnetic resonance investigations have shown the R-G-R inserts into the minor groove of DNA with flanking lysine residues in the AT-hook binding to the phosphate backbone of DNA [163–165]. Despite the extensive exploration of BRG1's helicase and bromodomain functions, the AT-hook domain has not been studied until recently and has gained attention for its distinct role in lineage commitment [61,166,167]. The AT-hook in the catalytic subunit of the SWI/SNF complex is part of a sub-category of AT-hooks called an extended AT-hook that is three times longer than other AT-hooks. The extended AT-hook has basic

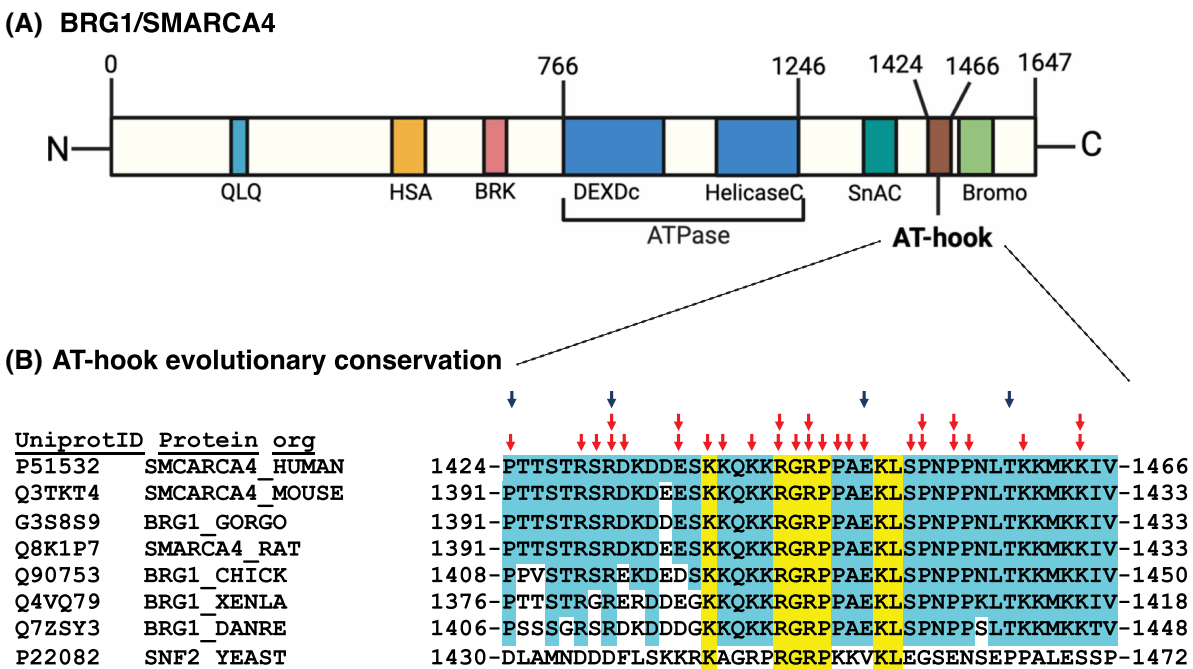

Figure 2. The AT-hook of BRG1 is evolutionarily conserved and targeted in various cancers and neurodevelopmental diseases.

(**A**) Domain organization of the human SWI/SNF catalytic subunit, BRG1 shown including AT-hook motif at the C-terminus. Number across the top of the schematic represents amino acid positions. (**B**) Amino acid sequence alignment shown for the AT-hook motifs in human BRG1 and its homologs in Mus musculus (mouse), Gorilla gorilla gorilla (GORGO), Rattus norvegicus (RAT), Gallus gallus (CHICK), Xenopus laevis (XENLA), Danio rerio (DANRE), *Saccharomyces cerevisiae* (YEAST). Conserved residues are highlighted in yellow and blue. Red arrows indicate amino acids mutated in one or multiple cancer types reported in cBioPortal and blue arrows indicate amino acids mutated in neurodevelopmental diseases as reported in SPARK, DECIPHER, ClinVar [168].

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residues symmetrically extending 12–15 amino acids from the core AT-hook motif (Figure 2) [169,170]. The AT-hook in yeast SWI/SNF has been shown to have an auto-regulatory function that stimulates the nucleosome-dependent ATPase activity. Loss of the AT-hook does not perturb complex integrity, SWI/SNF's affinity for nucleosomes or the ability of SWI/SNF to be recruited through the acidic activation domain of Gal4-VP16 [61]. The AT-hook associates with another regulatory domain inside the catalytic subunit and the N-terminal tail of histone H3, suggesting potential ways in which it could positively regulate SWI/SNF activity.

The AT-hook in the mouse esBAF complex appears to have a similar role as evidenced by naïve-specific binding of pluripotency TFs being lost when the AT-hook of Brg1 is deleted as measured by ATAC-seq[61]. There is a similar loss of epiblast specific TF binding in the primed staged with Zic2, Zic3 and Six4. Binding of the pluripotency TFs to sites that are in both naïve and primed stages or to their own genes cis-regulatory regions are not disrupted by loss of the AT-hook, the later as seen by the levels of Oct4, Nanog and Sox2 protein not being affected by loss of the AT-hook[61]. Consequently, loss of the AT-hook does not affect self-renewal or pluripotency maintenance, unlike that observed when Brg1 is completely deleted [129,143]. Brg1 colocalizes with TFs bound to naïve- and primed-specific sites and these regions are likely active naïve- and primed-specific enhancers based on their genomic location and co-localization with H3K27ac and H3K4me1. Monomethylation of lysine 4 of histone 3 is thought to be an early step in activating enhancers and at these regions also requires the AT-hook of Brg1. Brg1 binding at these enhancers is not reduced by deletion of the AT-hook, which rules out the physical presence of Brg1 being crucial for TF binding or for H3K4me1 and instead points to the reduction in catalytic activity being the crucial factor. These findings indicate that the AT-hook positively regulating Brg1's remodeling activity is vital for the establishment of stage-specific enhancers.

Brg1 and its AT-hook is also important for cell lineage priming as seen after removing LIF and the two inhibitors used to maintain cells in the naïve stage and allowing cells to differentiate spontaneously[61]. Ectodermal markers Sox1 and Nestin, mesoderm marker Tbxt and the endoderm marker Sox17 are all down-regulated in AT-hook deleted cells, consistent with defects in cell lineage priming. The endoderm-specific marker Gata4 is aberrantly highly expressed when the AT-hook is deleted. These findings indicate the potential role of AT-hook motif of Brg1 in early neuronal and cardiac development. These observations are consistent with conserved residues in the AT-hook domain being mutated in several cancers and neurodevelopmental diseases (Figure 2).

Mapping changes in the sites of active transcription in the naïve and primed stages reveals there are large-scale changes in transcription in both stages when the AT-hook is deleted that shows Brg1 has role in both activating and repressing transcription[61]. There are genes encoding factors important in cell lineage priming that fail to be activated in the primed stage when the AT-hook is deleted. These proteins are involved in such process like signaling, organ and anatomical development, cell communication, cell differentiation and neural differentiation. There are another set of genes that are normally active in the naïve stage that are shutoff in the primed stage that fail to be switched off when the AT-hook is absent[61]. Interestingly, these genes encode many of the same factors shown in Figure 1 discussed that are necessary to establish the unique metabolic state characteristic of the naïve stage (Table 1). These factors are needed for high levels of oxidative phosphorylation, ATP generation and lipid metabolism. Some of these proteins are required to repress glycolysis that are subsequently down-regulated in the primed stage to make glycolysis dominant in the primed stage. Last of all, factors important for shortening the cell cycle and G-protein coupled signaling in the naïve stage are not repressed in the primed stage when the AT-hook of Brg1 is deleted. The failure of these factors to not be transcribed in the primed stage represents a failure to dismantle aspects of the pluripotent state important in switching from pluripotency to cell lineage priming.

Conclusion

These studies for the first time indicate Brg1 has a critical role in cell lineage priming that is two-fold. One is to activate the necessary enhancers to transcribe the genes needed in the primed stage to make the factors needed for cell fate determination. The other surprising role of Brg1 is to repress expression of genes that encode metabolic, signaling and cell cycle factors that shape the pluripotent state, which need to be removed for cells to successfully exit pluripotency.

Perspectives

- The SWI/SNF ATP-dependent chromatin remodeler plays pivotal roles in development from pluripotency to terminal differentiation, making it difficult to separate its distinct functions. Mutagenesis of SWI/SNF often leads to various diseases, the most notable being cancer and neurological disorders and reflects its role in development.

- To more fully understand the role of SWI/SNF, it is important to not only study the effects of completely deleting its catalytic subunit. A key example of this is the study of SWI/SNF in cell lineage priming, which was not possible by merely deleting Brg1 and instead required attenuating its activity by deleting an autoregulatory domain.

- In the future more work is needed to understand the domains involved in both regulating the activity of SWI/SNF as well as those that help target SWI/SNF to its appropriate genomic sites in a cell-type specific manner to better understand its molecular basis in development and diseases.

Competing Interests
The authors declare that there are no competing interests associated with this manuscript.

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Abbreviations
ESC, embryonic stem cell; ICM, inner cell mass; TF, transcription factor.

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