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# SWI/SNF Chromatin Remodeling Complex in Regulating Mesenchymal Stem Cell Lineage Specification

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## Abstract

Mesenchymal Stem Cells (MSC) can be obtained from various tissues and differentiate into many different lineages, including osteoblasts, adipocytes, chondrocytes, cardiomyocytes, hepatocytes and neural cells both *in vivo* and *in vitro*. However, the ability of MSC to differentiate into specific lineages seems to be restricted and requires a deeper understanding of the genetic and epigenetic mechanisms. Epigenetic mechanism refers to a process that regulates heritable alterations in gene expression without changing the DNA sequence. SWI/SNF (SWItch/Sucrose Non-Fermentable), a chromatin-remodeling complex serves as an ideal intervention point for lineage manipulation of MSC. In this review, we discuss the importance of SWI/SNF chromatin remodeling complex in regulating the fate determination of MSC. We propose that selectively manipulation of subunits of SWI/SNF will enhance the lineage-specific differentiation of MSC and improve therapeutic application of MSC.

**Keywords:** SWI/SNF; MSC; Lineage commitment; Tissue engineering

## Introduction

Mesenchymal Stem Cells (MSC), also called multipotential stromal cells or mesenchymal stromal cells, are a heterogeneous subset of stem cells that can be isolated from various adult tissues, including bone marrow, adipose tissue and other sources [1-3]. Initial studies have showed that MSC are able to differentiate into the mesoderm cell lineages, including bone, cartilage, adipose tissue, skeletal muscle and cardiac tissue [1,4,5]. Recently, studies have also found that MSC can differentiate into endoderm and ectoderm lineages, such as hepatocytes, neurons, epidermal-like cells [6-8]. MSC are an outstanding choice for regenerative medicine, tissue engineering and clinical therapy. Differentiation of MSC is mediated by intrinsic and extrinsic regulatory mechanisms, including specific growth factors, signaling molecules and epigenetic modifications [9]. These regulatory factors together define a selective transcription of discrete combination of genes, which define a differentiation program and determine the specific lineage and phenotype. Better understanding of how specific lineage commitment is achieved and especially how epigenetic mechanisms take part in this process will facilitate the development of more effective protocols for MSC tissue engineering and cellular therapy. In this review, we summarize our current knowledge of how SWI/SNF chromatin-remodeling complex modulate multi-lineage differentiation of MSC.

## SWI/SNF chromatin-remodeling complexes

Gene transcription is dynamically regulated at different levels across a wide range of cellular processes, including stemness, differentiation and proliferation. The expression level of certain gene largely depends on the state of its associated chromatin. Histone modification enzymes or chromatin-associated multisubunit protein complexes can affect whether a gene is transcriptionally activated or repressed [10,11]. Based on the identity of their catalytic subunit, chromatin-remodeling complexes can be divided into four different classes, including SWI/SNF, ISWI, CHD and INO80 [12-14]. Switch/Sucrose Non Fermentable (SWI/SNF) enzymes are a family of evolutionarily conserved, multi-subunit complexes that depend on energy from Adenosine Triphosphate (ATP) to regulate the chromatin structure [15]. SWI/SNF complex consist either BRG1 or BRM, two alternative ATPases that catalyze the chromatin complex remodeling, along with 8-12 BRG1/BRM-associated factors (BAFs) [15]. BRG1 and BRM share 75% amino acid sequence identity and have similar domains: the QLQ domain (protein-protein interaction), the HSA domain (DNA binding), the ATPase domain and the bromodomain (acetyl-lysine histone mark recognition) [16].

The complexes share several common members, such as BAF170, BAF155, BAF60a/b/c, BAF57, BAF53a/b, BAF47, BAF45a/b/c/d and β-actin [17]. BRG1-containing complexes can be further classified into Polybromo-Associated Factor (PBAF) complexes, which uniquely contain BAF200 and BAF180 or BAF complexes, which uniquely contain BAF250A or BAF250B [16]. Among all BAFs members, BAF170, BAF155 and BAF47 are the functional core subunits for chromatin remodeling *in vitro* [15]. While other BAFs members are essential for interactions with transcriptional activators and repressors *in vivo*. The composition of SWI/SNF can be reconfigured during cell fate transitions through cell type-specific and developmental stage-specific expression patterns of certain subunits, which will be discussed in details later.

To regulate transcription activity, SWI/SNF chromatin-remodeling complexes are recruited by transcription factors to the promoters of target genes, where they can disrupt histone-DNA contacts and allow transcription factors to access their sequence-specific DNA [16,18]. Generally, SWI/SNF-mediated chromatin remodeling leads to sliding of nucleosome, eviction of nearby nucleosome or selective removal of H2A/H2B dimers near the Transcription Start Site (TSS) [18]. These

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activities modulate RNA Polymerase II occupancy and transcriptional initiation. Depending on whether a transcriptional activator or repressor recruits SWI/SNF, transcription can be up regulated or down regulated. The energy of ATP hydrolysis is harnessed to disrupt histone-DNA contacts and move nucleosomes away from the TSS or toward the TSS [16,18].

SWI/SNF is essential for self-renewal of stem cells and is critical for cell differentiation. Depletion of core subunits of SWI/SNF complexes, such as BRG1, BAF155 and BAF47, affects the survival of totipotent cells and leads to peri-implantation lethality in mouse [19-21]. Deficiency of BRG1, BAF155 or BAF250a/b impaired the ability of mESCs to differentiate into ectoderm, mesoderm and endoderm layers [22- 26]. BRG1 has been shown to co-occupy a large number of the genomic loci with OCT4 and SOX2 by ChiP-seq analysis, indicating the importance of SWI/SNF in regulating stem cell property [23]. The altered expression of BRG1 promoted the senescence of MSC with suppression of the NANOG transcription, which is part of the transcriptional circuitry governing stem cell functions. Overall, regulation of gene expression patterns during differentiation of any cell lineage requires cooperation with the SWI/SNF chromatin-remodeling complex [28].

## SWI/SNF and osteogenesis

Bone formation of MSC can be achieved by treatment of Bone Morphogenetic Proteins (BMPs) and Wnt proteins, which target a number of osteoblast-determining transcription factors, such as Runx2, Osterix (Osx), Id1, Dlx3 [29, 30]. Both Runx2 and Osx knockout mice fail to develop mature osteoblasts. Hence these two factors are widely accepted as master transcription factors for osteogenesis. Osx acts downstream of Runx2 during bone formation and regulates the expression of osteoblast markers, including collagen type I, Oestopontin (OP) and Osteocalcin (OC) [30]. Several studies have shown that SWI/SNF activity plays a critical role for induction of the osteoblast phenotype. For example, Brg1 is expressed in developing skeletal tissues of the mouse embryo and in *ex vivo* osteoblast cultures [31]. This expression of Brg1 depends on BMP2-induced Runx2 expression. Deficiency of Brg1 in calvarial cells and NIH3T3 cells impairs the expression of Alkaline Phosphatase (ALP), an early maker of osteoblast differentiation regulated by Runx2 [31]. BRG1 can be recruited to the promoter region OC via transcription factor C/EBPβ and activate the expression of OC mediated by RNA polymerase II [32]. During osteogenesis, Osx can recruit p300 and Brg1 to the promoter of it target genes to form transcriptionally active complex *in vivo*, which is enhanced by p38 [33]. Moreover, C/EBPβ-LAP* can interact with both Brg1 and Baf47 and bind to the Ric-8B promoter in differentiating osteoblasts, which causes repressed Ric-8B expression and osteogenesis [34]. The Retino Blastoma (RB) protein family plays a major function in the osteoblast lineage differentiation of MSC through directly target several osteogenic genes, incluing ALP. Both pRB and p107 can recruit BRG1 and RNA polymerase II to occupy the promoter region ALP gene and activate its transcription. However, the binding activities between pRB and p107 are mainly not overlapped [35].

## SWI/SNF and adipogenesis

MSC can be induced to differentiate into adipocytes under appropriate conditions. The commitment of adipogenic lineage requires upregulation of a variety of genes, which are largely mediated by the three classes of transcription factors, including peroxisome proliferator-activated receptor-γ (PPARγ), CCAAT/enhancer binding proteins (C/EBPs) and basic helix-loop-helix family (ADD1/SREBP1c) [36]. Chromatin remodeling is an important step in promoter activation during adipogenic lineage commitment and differentiation. For example, X/EBΠα, X/EBΠβ ανδ ΠΠΑΡγ2 require the modification of the chromatin structure by SWI/SNF ATPases BRG1 and hBRM to induce the adipogenic differentiation of uncommitted fibroblasts [38,39]. Moreover, depletion of BAF47, one of the core subunit of SWI/SNF, in murine 3T3-L1 preadipocytes and human MSC abrogates adipocyte differentiation through cooperation with C/EBPβ and PPARγ2 [40]. Study has shown that binding of Brg1 to PPARγγpromoter can be regulated by Prmt4 or Prmt5, members of protein arginine methyltransferases [40-43]. Furthermore, disruption of *Brd2* expression in mouse leads to elevated adiponectin expression in adipose tissue, suggesting Brd2 plays an important role in adipogenic regulation. Indeed, Brd2 can repress the activity of PPARγ and inhibit adipogenesis of 3T3-L1 pre-adipocytes [44]. Characterization of genes associated with adipocyte development using microarray analysis revealed that BAF47 is upregulated in this induction. Importantly, even though BRM is dispensable for normal development, this gene is critical for balance of lineage selection between osteoblasts and adipocytes of MSC. BRM depletion favors osteoblast lineage of MSC over adipocyte lineage, which is confirmed by BRM knockout mice that display resistance to age-related osteoporosis [45].

## SWI/SNF and chondrogenesis

During developmental stage, chondrocytes derive from mesenchymal progenitors and express cartilage-specific collagens II, IX and XI. The differentiation of chondrocytes is subject to complex regulation by interplay of the transforming growth factor β, Wnt, BMP and fibroblast growth factor (FGF) signaling pathways [46]. The current known master transcription factor in regulating chondrogenesis is Sox9, which is expressed predominantly in the mesenchymal condensations during the early development of embryonic skeletons [47]. In mouse chimaeras, $Sox9^{-/-}$ cells are excluded from all chondrogenic tissues but are present as juxtaposed mesenchymal cells that show no expression of the chondrocyte-specific markers [48]. Previous studies showed that SWI/SNF-mediated chromatin remodeling complexes are enriched in cartilage-expressed transcripts, which are identified by comprehensive mapping [49]. Through downstream mediator Sp1, BMP2 can induce expression of FGF receptor 3 (FGFR3), which is essential for cartilage development. Importantly, Brg1 is shown selectively remodel a Sp1-binding sites-containing chromatin region locates in the transcription start site of FGFR3 and induces FGFR3 expression [50].

## SWI/SNF and cardiomyocytes

Adult cardiomyocytes have little or no regenerative ability. It is challenging to efficiently differentiate multipotential stem cells into cardiomyocytes. In general, FGF2, Activin A, BMP4, vascular endothelial growth factor (VEGF) and the Wnt inhibitor DKK-1 can promote the differentiation of cardiomyocytes [52]. Multiple transcription factors, including GATA4, MEF-2, NKX2.5, HAND1, HAND2 and TEAD, are predominantly expressed in myocardium and regulate the expression of cardiac genes. Study has found that BRG1 can interact with LIM-only protein CRP2 and induce expression of smooth muscle genes in adult cardiomyocytes [52]. Deficiency of BAF250a causes early development arrest and missing of mesoderm layer in mouse embryos [22,53]. BAF250a is required for mouse ESC to differentiate into mesoderm-derived functional cardiomyocytes and adipocytes, while dispensable for ectoderm-derived neuron formation [22]. Deletion of Baf250a in the sinoartial node, the region responsible for heart beating, leads to de-repression of Nkx2.5 and causes sick sinus diseases, indicating a critical role of Baf250a in normal heart function

[54]. Mechanistically, BAF250a directly interacts with subunits of Nucleosome Remodeling and Histone Deacetylase (NURD) and occupied the regulatory regions of cardiomyocyte associated genes [53]. In addition, Baf60c can collaborate with cardiomyocyte-specific transcription factors Gata4 and Tbx5 to promote the cardiomyocyte differentiation when Nodal/BMP signaling pathways are inhibited [55].

### SWI/SNF and hepatocytes

Hepatocyte-like cells generated from MSCs serve as a promising cell source for liver regeneration or tissue engineering. However, how to improve the efficacy and consistency of hepatic differentiation from MSCs remains challenging. Previous studies have revealed that The SWI/SNF chromatin-remodeling complex is essential for hepatocyte differentiation. For example, study has showed a differentiation-specific up-regulation of BRM expression in hepatocytes and C2C12 cells, which is mediated by transcription factors C/EBPβ, GATA2 and GATA3 [56]. During the early stage of liver development, BRG1 or BRM can repress the expression of tryptophan oxygenase, a late stage-specific gene [57]. As liver cells differentiate, the expression of BRM is gradually up-regulated while BRG1 is down-regulated. Deficiency of BRG1 and BRM leads to compromised expression of albumin gene in hepatocytes. BRM and BRG1 directly bind to the promoter region of the albumin gene, along with RB family proteins and C/EBPα [58]. The sumoylation of C/EBPαα can block the interaction between C/EBPα and BRG1, which inhibits the proliferation of hepatocytes [59]. BRG1 and BRM are also involved in transcription of ATP-binding cassette transporter A1 (ABCA1) through associated with liver X receptor (LXR) and retinoid X receptor (RXR) in Hep3B cells, a hepatocyte cell line [60]. Deletion of BAF47 in mouse hepatocytes leads to neonatal lethality due to severe hypoglycemia, glycogen storage failure and impaired energetic metabolism. Loss of BAF47 is accompanied by downregulation of a majority of liver development genes [61]. BAF60a, together with PGC-1α, can induce the expression of PPARααtarget genes and stimulate fatty β-oxidation in hepatocyte [62].

### SWI/SNF and neurogenesis

MSC have a capacity to differentiate into neurons and astrocytes when treated with retinoic acid and brain-derived neurotrophic factors [63]. Previous reports have demonstrated that mutations in Brg1 and its associated proteins lead to development of neuronal disorders [64, 65]. During neuronal differentiation, BAF53A is repressed and replaced by BAF53B, suggesting SWI/SNF activity is tightly regulated for proper development of neuron [66]. Indeed, conditional depletion of BAF subunits in mice found that the Brg1 and BAF complex play an essential role at various steps during neurogenesis [66]. These mice display a neonatal lethal phenotype and have thin cortices. Specific depletion of BAF53b showed dramatic defects in dendritic development and memory [67]. Brg1 and other BAF subunits mutant mice showed decrease of proliferation in neural progenitors and growth retardation in cerebellum [68, 69]. These genetic studies provide useful insights to BAF functions in neurogenesis and are helpful for designing more efficient strategy for differentiation of MSC to neural lineage.

### Small-molecules targeting SWI/SNF complex

Overall, our understanding of epigenetic regulation on MSC differentiation could be beneficial for developing better strategy of regenerative medicine. Targeting BRM in MSC display a dramatic effect on promoting osteoblast lineage rather than adipogenic lineage, demonstrating great potential of SWI/SNF chromatin-remodeling complex as therapeutic targets for stem cell-based regenerative medicine and the treatment of human metabolic disease such as osteoporosis and obesity [45]. Indeed, the screening of small cell-permeable inhibitors of SWI/SNF chromatin-remodeling complex has been intensively pursued over the last decade. For instance, inhibitor I-BET151 can specifically bind to the bromodomains of BRD3/4 and inhibit the transcription of target genes [70]. Importantly, many subunits of SWI/SNF chromatin-remodeling complex contain this druggable bromodomains, including BRG1, BAF190B, BRD9 and BAF180. Hence, the strategy of using small molecule inhibitors in combination with lineage-specific induced medium will help the cell-based therapeutic approach generating promising results.

## Conclusion

As a solution for the low regenerative capacity of adult tissues, MSC has attracted many researchers' attention for its self-renewable and pliable traits. By using MSC, donor site morbidity and immune reactions can be overcome. A critical caveat in the field is the relatively poor understanding of the molecular mechanisms that governing MSC self-renewal and lineage specification. Here, we propose that differentiation efficiency of MSC into cell types of interest will be dramatically improved by altering the composition of SWI/SNF components. As discussed above, ectopic expression of subunits of SWI/SNF complex can lead to activation of tissue-specific transcriptional program and drive cell fate selection or convert one cell type into another. In addition, more and more data suggest that the combinatorial composition of mutually exclusive BAF members in different SWI/SNF complex determine their binding ability for lineage-specific transcription factors. Pharmacological targeting of the SWI/SNF complex of MSC and its progeny represents a novel strategy for enhancing tissue-engineering and cell-based therapy.

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