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Role of brahma-related gene 1/brahma-associated factor subunits in neural stem/progenitor cells and related neural developmental disorders

Ke NY *et al.* BAF complex subunits in NSPCs

⁶ INTRODUCTION

Neural stem/progenitor cells (NSPCs) are self-renewing neural cells capable of differentiating into neurons, astrocytes and/or oligodendrocytes^[1-3]. During development, NSPCs are critical for the establishment of the central nervous system (CNS)^[4-6]. In the adult central neural system, neurogenesis plays a key role in fundamental processes, for example, memory, learning, the maintenance of normal tissue homeostasis, and the autonomous repair of pathological brain tissues^[7,8]. NSPCs can be isolated from three canonical neurogenic niches in the spinal cord and brain, namely, the central canal (CC) in the spinal cord, the subgranular zone (SGZ) of the dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricle (LV) in the brain^[9-13]. In addition, NSPCs have been identified in the developing cerebral cortex^[14], olfactory epithelium^[15] and outside the CC^[16]. The fact that NSPCs can be isolated and propagated *in vitro* opens up new opportunities for medical research, and we hope they can be used to compensate for cell loss that features in several serious neurological disorders. Moreover, NSPCs can be created *in vitro* through induced differentiation from induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), expanding the pool of models for studying stem cells in health and illness^[17,18]. For cell-based therapy approaches targeting the brain and spinal cord, NSPCs have emerged as focal points. However, the small amount of NSPCs present in this tissue has restricted the clinical uses of these cells. Although recent advancements in ESCs and iPSC research have meant that these cells can be novel sources of NSPCs, understanding NSC molecular regulation and NSPC applications, which are important for disease modeling and regenerative medicine, remain challenges^[19-21].

11

The BRG1/BRM-associated factor (BAF) complex, which is a mammalian chromatin remodeler, regulates chromatin structure and transcription by providing subunit organization and nucleosome recognition in an ATP-dependent manner. Structurally, the BAF complex contains three modules, an ATPase, an actin-related protein (ARP) and a base module^[22]. More than 30 major subunits of these modules can combine to form the complex^[22-24].

By controlling chromatin structure, controlling the differentiation of NSPCs to produce different types of brain cells, and regulating transdifferentiation between cell types, BAF complexes perform crucial roles in the maintenance of a gene expression program. At various phases of brain formation, BAF complexes have specific roles and seem to be produced by the combinatorial assembly of their subunits. Moreover, intimate interactions between the BAF chromatin-remodeling complex and transcriptional machinery control the development of NSPCs^[25]. With the combinatorial assembly of homologous component families, which enables their nonredundant functions, distinct BAF complex structures are made possible. ESCs, NSPCs, and postmitotic neurons all exhibit developmental stage-specific BAF assemblages during mammalian brain development. Neuronal BAF (nBAF) function is required for the development of mature postmitotic neuronal features along with long-term memory, and neural progenitor-special BAF (npBAF) structures are particularly important for modulating the rates and modalities of neural progenitor cell replication. Given the high prevalence of BAF subunit mutagenesis in neurological illnesses, it is obvious that BAF complexes perform a crucial role in controlling the rate of neuronal development, homeostasis, and plasticity. Understanding how BAF complex subunits influence BAF complex function and the roles played by different subunits will reveal disease pathogenesis and lead to novel treatments for related human disorders ultimately^[26,27].

Here, we summarize recent progress in comprehending the role of the BAF complex in NSPCs. We focus on NSC-/NPC-specific BAF complex subunits and describe how they determine the balance between the self-renewal and differentiation of NSCs and are involved in several human neural developmental disorders.

BAF COMPLEX SUBUNITS AND THEIR MAIN CHARACTERISTICS IN NSPCs

Among the major BAF complex subunits, there are 12 subunits expressed in NSPCs in the embryo cortex, olfactory bulb (OB) and spinal cord, adult brain and spinal cord, and human and mouse retina (detailed information and references are shown in Table 1).

BAF190A (BRG1/SMARCA4)

Brg1 (Brahma-related gene 1) is necessary for NSPCs to remain in a state where they can react to gliogenic signals and to suppress neuronal commitment. Lack of Brg1 in NSPCs led to precocious neurogenesis, such that cells in the ventricular zone developed into postmitotic neurons before the start of gliogenesis in conditional *brg1*-mutant mice. As a result, these animals significantly lost the ability to differentiate astrocytes and oligodendrocytes. In addition, *in vitro* Brg1 deletion reduced growth factor-induced astrocyte development in gliogenic progenitors. Furthermore, it has been discovered that the levels of proteins associated with stem cell maintenance, such as Pax6, Sox1, and Musashi-1, are significantly lower in the ventricular zones of the mice with *brg1*-mutations^[28]. The hippocampus experienced abnormal adult neurogenesis as a result of Brg1 deletion in nestin-expressing NSPCs. This abnormal adult neurogenesis initially decreased the number of adult NSPCs in the hippocampus, inhibited progenitor maintenance, and later decreased NSPC responsiveness to physiological stimulation. Brg1 deletion appears to hinder cell cycle progression mechanistically, which is partly because of increased p53 pathway activation and p21 expression. Defects in neurosphere formation brought on by Brg1 deletion were repaired by knocking down p53. These findings suggest that aNSPC and progenitor cell maintenance and responsiveness during neurogenesis are determined by epigenetic chromatin remodeling *via* a Brg1- and p53/p21-dependent mechanism^[29].

Many transcription factors manipulating neurogenesis have been ascertained in the adult and developing brain, and notably, the neurogenic transcriptional regulation factor Pax6, which can directly interact with the Brg1-carrying BAF complex in adult

neural progenitor cells. Abolition of either Pax6 or Brg1 in the subependymal zone (SEZ) caused the offspring of adult NSPCs to switch to the SEZ ependymal cell lineage. In the interim, shifting neuroblasts changed to distinct glial cell lineages during or after reaching the OB. Several studies have revealed that there is a network with tripartite effector programming neuronal fate, which can be activated by Pax6-BAF and promote neurogenesis and the transformation from glia to neurons. According to the whole-genome analysis, the downstream regulatory factors of Pax6-BAF include Nfib, Sox11 and Pou3f4. While Brg1 is absent in SEZ and OB, the binding sites of Pax6 carried by Brg1 and most down-regulated genes will be down-regulated at the same time^[30]. In the study of Jayaprakash, S., *et al.*, they find that Brg1 appears as a slender spherical structure so that it can provide a larger surface and form the further complex by binding to BAF57 and BAF60A. Furthermore, a neural Brg1 isoform interacts with the central neurodevelopmental transcriptional repressor REST/NRSF, suggesting that Brg1 can interact with transcription regulators and factors to conduct the BAF complex to specific sites^[31].

BAF155 (SMARCC1) and BAF170 (SMARCC2)

Recent study found that conditional deletion of BAF155 can lead to the decrease of basal intermediate progenitors (bIPs), while the delamination of apical radial glial progenitors (RGs) can cause the increase of basal RGs (bRGs). During the progress, BAF155 has been proved necessary for the normal activity of PAX6 to regulate the gene expression. BAF155 can control the expression of the CDC42 effecting protein CEP4 in the Pax6-dependent way in order to regulate the stratification of progenitor. In addition, BAF155-dependent chromatin remodeling is also involved in regulating several human RG-specific genes, thereby acting on the generation of basal progenitors (BPs)^[32].

The study of Narayanan *et al.*^[33] in 2015 revealed a molecular mechanism of controlling the global chromatin state and transcriptional program during development, which is mediated by the BAF complex. They found that BAF155 and

BAF170 knockout can cause elimination of the entire BAF complex with all kinds of BAF subunits in cortical development, with the overall increase of the abundance of the repressive marks (H3K27me2/3), decrease of active chromatin mark H3K9Ac, and down-regulation of gene expression. Both BAF155 and BAF170 subunits are expressed in early cortical progenitors (E10.5-E14.5), and BAF170 is replaced by BAF155 in late cortical progenitors^[34]. Specifically, between E12.5 and E14.5, apical progenitors express BAF170 and BAF155. They exhibit comparable expression patterns at the height of upper layer neurogenesis (E15.5), with BAF170 being missing from VZ progenitors but expressed in the cortical plate but expressed in the cortical plate^[34]. While BAF170 overexpression resulted in the acquisition of a feature similar to that acquired by the Pax6-loss brain, with depletion of overlying layer neurons, BAF170 loss in Emx1 cortical progenitors exerted an effect opposite to that of Pax6 elimination and caused an aberrant growth of IPs and a bias toward the acquisition of an overlying layer identity^[34]. By the recruitment of the transcriptional suppressor REST to Pax6 targets, the BAF170-containing npBAF complex indirectly suppresses neurogenesis in its early stages^[34,35]. Interestingly, the transcription of BAF170 and Brm subunits, which replace BAF155 and Brg1 subunits in the esBAF, respectively, begins at the same time when ES cells commit to developing into neural progenitors^[33,36]. According to a recent functional investigation, Pax6 directly associated to the BAF complex in aNSCs that contained the Brg1, and its neurogenic activity was abolished in the lack of the Brg1^[30]. BAF170 and BAF45 also carry domains with putative DNA-binding capacities^[37]. In the neonatal DG, the BAF170 member of the complex is found in radial glial-like (RGL) cells and cell types implicated in following stages of adult neurogenesis together with mature astrocytes. The pool of RGL cells in the DG is reduced by conditional knockout of BAF170 during late cortical neurogenesis and also adult brain neurogenesis, which encourages terminal astrocyte differentiation. A moderate loss in spatial learning was produced by the induced abolition of BAF170 in the DG throughout adult brain neurogenesis, with the reversal test showing the greatest impact on spatial learning. These findings indicate a specialized role for adult neurogenesis in the DG regulating

adaptive behavior and show the engagement of BAF170-reliant chromatin modification in neurogenesis and cognition of hippocampus^[38].

BAF250A (ARID1A)

The core ATPase, Brg1 or Brm, BAF250A or BAF250B, a homologous dimer of BAF155, or a heterologous dimer of BAF170 and BAF155 are just a few examples of the different subunits that npBAF can contain^[27]. Mammal BAF has significantly different from its yeast analogue, losing some members while obtaining new core members, such as BAF45a/b/c/d, BAF57, BAF250A/B, SS18/CREST, beta-actin, BRD7, and BRD9. Notably, BAF250A/B are the most commonly mutated subunits of BAF complex in related human neurological diseases^[36]. Loss of BAF250A or BAF250B in mouse models leads to early embryonic lethality^[39], indicating that, despite their homology, both genes are essential for early development.

Recent genome sequencing and many clinical studies have revealed that mutations of BAF250A is closely related to microcephaly and mental retardation. Liu *et al*^[40] generated a *baf250a* conditional knockout mouse line and found that cortical thickness was reduced in the developing cortex. Radial glial cell proliferation is inhibited by loss of BAF250A function, which also increases the rate of cell damage during late cortical neurogenesis and causes abnormal expression of genes involved in proliferation and differentiation. Therefore, for the purpose of better understanding the pathogenic mechanisms and creating new treatments for neurodevelopmental disorders brought on by its mutations, BAF250A may be one of the gene possibilities that is worthwhile being researched^[40].

BAF45A and BAF45D (DPF2)

BAF45 family proteins, include BAF45A, BAF45B, BAF45C and BAF45D, are subunits of the BAF complex^[41]. BAF45A, an npBAF, is required for the self-renewal and proliferative features of neural cells^[41]. BAF45A is identified in olfactory neural stem cells (oNSCs), E10.5-E11.5 cortical NPCs, and E10.5-E16.5 spinal cord ventricular zone

NSCs^[15,41]. BAF45D is expressed in the SGZ of the LV, SGZ of the DG, and the CC of the adult spinal cord. Co-expression of BAF45D and glial fibrillary acidic protein (GFAP), a marker protein of radial glial cell-like cell was found in the SGZ, SVZ, and CC of the adult spinal cord. According to the results of quantitative examination, BAF45D is selectively expressed in the adult neurogenic regions of neurons in CNS. What's more, BAF45D is necessary for the induction of PAX6, a determinant for neuroectoderm that regulates adult neural stem/progenitor cell self-renewal and specific neural fate, during neuroectodermal differentiation of H9 cells^[42].

Recently, BAF45D has been shown to regulate spinal cord neural stem/progenitor cell (SCNSC/SCNPC) fate mediated through the SMAD-PAX6 axis. SCNSCs exhibit increased DNA-BAF45D compared to that in human ESCs^[43]. It has been reported that postmitotic neurons express BAF45B/C protein but lack the paralogous BAF45A/D, which confers neuronal properties^[25-27,41]. The protein expression of BAF45D in adult rat NSPCs and neurons but not astrocytes may imply a role for BAF45D in the differentiation of NSPCs^[44].

BAF53A (ACTL6A)

The BAF53 subunit is encoded by the BAF53A (ACTL6A) or BAF53B (ACTL6B) gene, with the latter exclusively expressed in differentiated neurons^[41].

BAF53A is specific to the npBAF complex and can be replaced by BAF53B in the nBAF complex in neurons^[26,45]. miR-9 and miR-124 control the transition of postmitotic neurons from the BAF complex's BAF53A to BAF53B subunit^[46]. These miRNAs' expression is derepressed in neurons during cell development, which encourages the replacement of BAF53B in the nBAF complex by suppressing the expression of BAF53A. Increased progenitor proliferation can result from BAF53A's continued expression^[46]. These miRNAs have an interacting location in the 3'UTR of BAF53A, and their expression is constrained in progenitors by REST and its corepressors^[47]. As a result of decreased chromatin accessibility at particular neural transcription factor-binding sites

brought on by BAF53A loss, cell cycle-related genes are repressed, preventing the advancement of the cell cycle and cell differentiation^[48].

BAF57 (SMARCE1)

BAF57, subunit in the BAF complex core, is highly conserved in the BAF complexes of vertebrates^[49]. The DNA-binding capabilities of its primary structural characteristic, a high-mobility group domain, imply that BAF57 may perform topological functions when the BAF complex moves in or out a nucleosome. BAF57 specifically interacts with a variety of proteins which aren't part of the BAF complex. BAF57 demonstrates particular functionalities as a result of these interactions. For example, in the embryo, it interacts with the transcriptional cosuppressor Co-REST to enable the neuronal genes inactivation in nonneuronal cells throughout development^[50]. Interestingly, global gene expression profiling results indicated that BAF57A was specifically upregulated in human NSPCs of OB (OBNSPCs) but not in human embryonic NSPCs (hENSC)^[51]. In cultured NSCs, BAF57 interacts with the overexpressed intracellular domain of neuregulin-1 and leads to a decrease in the NSC proliferation rate^[52].

BAF60A (SMARCD1)

The BAF60A/B subunits define an ESC-specific assembly of BAF, named esBAF^[27]. The BAF subunits BAF60A binds to BRG1, the primary factor that drives the BAF complex to particular genomic locations, and interacts with transcription regulators and factors^[31]. Nuclear receptors and the BRG1 complex may have an additional important and direct relationship that is necessary for recruitment of promoter and subsequent chromatin modification^[53]. Low levels of BAF60A and BAF45B/D expression are found in oligodendrocyte precursors, and these expression levels are upregulated upon differentiation^[54]. However, their specific roles in NSPCs are still unclear.

BAF60C (SMARCD3)

During development, another crucial BAF complex component called BAF60C also has neuronal progenitor-specific actions. BAF60C is expressed in neural progenitors in the mouse and human retina, as well as the human cortex and spinal cord^[55]. BAF60C expression decreases during neural differentiation, and through its interaction with the Notch pathway, its overexpression keeps progenitors in a proliferative condition. Finally, Muller glia that resume the cell cycle following neurotoxic damage express BAF60C once more^[55].

BAF55A (SS18)

BAF55A, also called SS18, is a member of the npBAF complex. In NSCs, SS18 knockdown results in cell cycle exit and self-renewal failure^[48]. Moreover, SS18 is adaptively activated to respond to ethanol exposure, protecting fetal NSCs against complete loss of miR-9-2^[49].

BAF47

BAF47, a ubiquitous BAF complex subunit, is expressed in oNSCs^[15]. However, the exact function of BAF47 remains largely unknown.

BAF COMPLEX FUNCTIONS IN BALANCING SELF-RENEWAL AND DIFFERENTIATION OF NSPCS

⁸ The number of neural stem cells expands through symmetrical division, and through asymmetrical divisions, they maintain the capability to self-renew and produce other differentiated cells^[56]. Normal neural development requires the maintenance of the dynamic balance between the proliferative cells and differentiated cells of neural stem cells, which controls the number of stem cells and neurons and protects the body from diseases such as glioblastoma^[57]. Furthermore, neural stem cells respond to several molecular signals during neurogenesis, especially those mediated by the Wnt and Notch signaling pathways^[58]. For instance, Notch signaling is a significant mechanism regulating the balance between the quiescence and differentiation of neural stem

cells^[59]. By suppressing the Notch pathway, the homeostasis of neural stem cells can be altered, promoting neural differentiation^[60].

Several BAF family members, which act as components or modulators of the Notch and Wnt/ β -catenin signaling pathways, have been shown to exert either positive or negative effects on the differentiation of neural stem cells^[55,61]. On the one hand, neural differentiation can be promoted by BAF155 and BAF170, which act on regulators of Wnt/ β -catenin signaling-related genes, including H3K27me3 and H3K4me2^[15,62]. On the other hand, BAF45a and BAF53a contribute to the proliferation and self-renewal of neural stem cells^[41]. The repression of BAF53a during neural differentiation is realized through its 3'-UTR and the cooperative influence of miR-9 and miR-124^[45]. Brm and BAF57 interact with the neuregulin-1 (Nrg-1) intracellular domain, reduce proliferation and promote differentiation of neural stem cells in vitro, possibly by reversing the direction of signaling in a pathway^[63]. Furthermore, it has been shown that the overexpression of BAF60c maintains the proliferation of neural progenitors by interacting with the Notch signaling pathway^[55]. The BAF complex may also make direct contact with the neurogenic transcription factors that are critical for neural stem cell specification or differentiation. Notably, the subunit composition of BAF complexes undergoes a profound switching during differentiation; for instance, BAF40c is replaced by BAF40a, the function of which is activated by Pax6, Tbr1, and Tbr2^[64]. Moreover, BAF155 in the primate brain has been shown to be involved in the normal activity of Pax6, thereby regulating the specification of progenitors during cortex development^[32].

Overall, BAF complexes function as both agonists and inhibitors of neural differentiation. Notably, certain similarities and differences have been revealed through the approaches used in the aforementioned studies. A study by Narayanan *et al*^[32] was carried out by generating cortex-specific BAF155-knockout mice, while in another study, Nguyen *et al*^[62] adopted a transgenic mouse model in which both BAF155 and BAF170 were knocked out, eliminating the entire BAF complex during late cortical neurogenesis. Their double-knockout model offered a novel and practical method for examining the function of complete BAF complexes during cerebral development^[65].

Furthermore, a study by Bi-Lin *et al*^[66] was conducted after the neural crest-specific knockout of BAF155 and BAF170 in Wnt1^{Cre/+} and Pax3^{Cre/+} mice, and the results demonstrated that the BAF complex modulated the gene expression network and pathways, including the Notch signaling pathway, critical for neural crest development.

NSPC-RELATED BAF COMPLEX SUBUNITS IN NEURAL DEVELOPMENTAL DISEASES

Given the importance of BAF complexes in creating and sustaining a chromatin state that keeps proper transcriptional output during NSPC proliferation, differentiation and responses to exogenous or endogenous stimuli, it is clear that several neural developmental disorders have been linked to NSPC-related BAF complex subunits (Table 1 and Figure 1).

Coffin-Siris syndrome

¹⁰ Coffin-Siris syndrome (CSS) is a unusual congenital neural developmental disorder characterized clinically by intellectual disability (ID), progressive facial thickening, hirsutism, recurrent infections, difficult feeding, and restricted growth of the distal fifth phalanx and nails^[67,68]. Genes encoding NSPC-related BAF complex subunits have been found to have mutations recently thanks to extensive human exome sequencing and genome-wide association research, including BAF45D^[69-71], BAF47^[72-74], BAF57^[67,75,76], BAF60A^[77], BAF170^[78], BAF190A/BRG1^[72], and BAF250A^[72]. Different brain midline abnormalities, similar to those seen in people with CSS, were shown to be caused specifically by BAF47, BAF57, and BAF250B mutations in mice with a heterozygous neural system-specific SMARCB1 defect and a partial dysfunctional mutation in a BAF core member gene, indicating significant clinical suggestions for BAF complex-related ID/neurodevelopmental diseases^[79].

Within a cohort of 15 unrelated individuals on the CSS pathway disorders registry, who were carriers of a SMARCA4 variant, they showed differences in the severity and number of learning disabilities and health problems. Two of them with novel nonsense

variants appeared to acquire a non-organ/system affected phenotype with minor learning/behavioral differences^[80]. A recent report described a Chinese woman presenting with on the CSS pathway disorders registry, who were carriers of a SMARCA4 variant, they showed differences in the severity and number of learning disabilities and health problems. Two of them with novel nonsense variants appeared to acquire a non-organ/system affected phenotype with minor learning/behavioral differences and endocrine dysfunction. Whole-exome sequencing was used and led to the identification of a heterozygous missense variant in the SMARCC2 gene of the proband^[81].

Nicolaides-Baraitser syndrome

12

The clinical features of patients with nicolaides-Baraitser syndrome (NCBRS) caused by mutations in the SMARCA2 gene, remarkably resemble those of CSS patients^[82]. The characteristics of hands and feet are where NCBRS and CSS most clearly diverge. While typical CSS patients have hypoplasia or agenesis of the fifth fingernail with or without engagement of the nail phalanges, typical NCBRS patients have pronounced distal phalanges and interphalangeal joints^[75]. Five individuals with mutations in BAF60A exhibited developmental delay, small hands and feet, hypotonia, ID, and difficult feeding. According to TRIO exome sequencing, these mutations developed in four of the five patients^[77]. A missense mutation (p. Arg366Cys) of BAF47 also has been reported to be associated with NCBRS^[75]. Furthermore, variants in BAF170 have also been found in patients presenting with overlapping ID syndromes related to other BAF subunits, such as those identified in CSS and NCBRS^[78].

Autism spectrum disorder

Autism is a neurodevelopmental disease which is caused by both environmental and genetic factors, presented as speech problems, limited and repetitive behaviors and social skills barrier^[83]. Recent exome-sequencing studies on individuals with autism

have found mutations in the BAF155, BAF170^[84] and BAF190A^[85] genes. But at least seventy percent of the cases, the fundamental genetic cause is still unknown.

Kleefstra syndrome spectrum

Kleefstra syndrome spectrum (KSS) is a recognizable syndrome characterized by ID and induced by a hybrid ⁷ mutation in the euchromatin histone methyltransferase 1 (EHMT1) gene^[86,87]. According to the research of Kleefstra *et al*^[88], KSS could result from mutations in any complex protein including MLL3, MBD5, NR1I3, BAF47, or EHMT1. The EHMT1 mutation is not present in every patient with the primary symptoms of Kleefstra syndrome. In fact, de novo mutations in four genes that code for epigenetic regulators, including BAF47 (SMARCB1), were found in four of the nine individuals who did not have EHMT1 mutations^[88]. And their research using a *Drosophila* model showed that MLL3, MBD5, NR1I3, BAF47, and EHMT1 directly interact with one another^[88].

CONCLUSION

Considering recent research progress, we suggest that three aspects of BAF complexes should be investigated in the near future. First, BAF complexes are crucial for development of neural system and differentiation of neural cells, including the specification of neural fate and functionality^[4]. BAF complex subunits play key roles in the manipulation of gene expression, and the distinct ontogenetic stage-specific BAF complex functions in neural stem/progenitors and postmitotic neuronal cells that are derived from the combinatorial organization of these subunits^[26]. Sequencing of human whole-exome and genome-wide association studies have recently demonstrated the link between mutants of BAF complex subunits and neurodevelopmental illnesses like CSS, NCBS, KSS and autism spectrum disorder (ASD)^[89-92]. Focus must be placed on the roles played by BAF complex organization during neural development as well as the ways in which mutations in well-known BAF complex subunits contribute to certain neurodevelopmental illnesses^[93]. Secondly, both loss- and gain-of-function techniques

to evaluating neural network development at the molecular, single-cell, and network activity levels should be used in order to comprehend how BAF complex gene mutations might cause the phenotypic convergence of CSS, NCBS, KSS, and ASD. For example, ASD and KSS genes focus primarily on the level of neural network communication and provide insight into the pathophysiology of phenotypic consistency disorders^[79,94]. Thirdly, recent investigations have shown that BAF complexes are frequently involved in human cerebral development abnormalities, providing fresh mechanisms and corresponding paths for therapeutic intervention, all of which should be looked into. In recent years, small compounds that target the BAF complex subunits have become viable therapeutic agents. Researchers in the field have been motivated to recognize and take use of the whole spectrum of therapeutic options as a result of the creation and evaluation of novel drugs that target a variety of BAF complex subunits^[95].

Figure Legends

Figure 1 BRG1/BRM-associated factor complex subunits in neural stem/progenitor cells and the related neural developmental diseases. The BRG1/BRM-associated factor (BAF) complex subunits in neural stem/progenitor cells are shown (in colors), including BAF45A/D, BAF47, BAF53, BAF55A, BAF57, BF60A/C, BAF155, BAF170, BAF190A, and BAF250A. The other two types of the BAF complex subunits, β -actin and BCL7/A/B/C, are shown in grey. Neural developmental disease types are listed as, I: Coffin-Siris syndrome; II: Autism spectrum disorder; III: Kleefstra syndrome; IV: Nicolaides-Baraitser syndrome; “?”: Unknown. BAF: BRG1/BRM-associated factor.

Table 1 BRG1/BRM-associated factor complex subunits in neural stem/progenitor cells

BAF complex subunits(alias)	NSPC types	Function	Interaction	Related neural developmental diseases	Ref.
BAF45A (PHF10)	oNSC,	E10.5-E11.5 NSPC proliferation	BRG1	-	Bachmann <i>et al</i> ^[15] , 2016; MacDonald <i>et al</i> ^[89] , 2022; Lessard <i>et al</i> ^[41] , 2007
	cortical NPCs,	E10.5-			
	E16.5 spinal cord VZ				
BAF45D (DPF2)	SGZ, SVZ, spinal cord	PAX6 expression,	PAX6, BRG1	CSS	Liu <i>et al</i> ^[42] , 2017; Wang <i>et al</i> ^[44] , 2019; Chen <i>et al</i> ^[43] , 2022; Vasileiou <i>et al</i> ^[69] , 2018; Knapp <i>et al</i> ^[70] , 2019; Milone <i>et al</i> ^[71] , 2020
	central canal GFAP +	contributes to NSPC			
	radial glial cells	induction			
BAF47 (SMARCB1)	oNSC	-	BRG1	CSS, kleeftstra syndrome,	Bachmann <i>et al</i> ^[15] , 2016; Tsurusaki <i>et al</i> ^[72] , 2012; Santen <i>et al</i> ^[74] , 2013; Wieczorek <i>et al</i>
				Nicolaides-Baraitser	

				syndrome	<i>al</i> ^[75] , 2013; Kleefstra <i>et al</i> ^[88] , 2012; Gossai <i>et al</i> ^[73] , 2015
BAF53A (ACTL6A)	oNSC, NPCS in the neural tubes of E11.5 embryos	BAF53A is essential for proliferation	miR-9 and NPC 124	-	Bachmann <i>et al</i> ^[15] , 2016; Lessard <i>et al</i> ^[41] , 2007; Yoo <i>et al</i> ^[45] , 2009
BAF55A (SS18)	NPCs in VZ	SS18 is required for NSC self-renewal	BRG1	-	Staahl <i>et al</i> ^[48] , 2013
BAF57 (SMARCE1)	Adult human OBNSCs	NSC proliferation	Neuregulin-1	CSS	Wieczorek <i>et al</i> ^[75] , 2013; Kosho <i>et al</i> ^[67] , 2014; Marei <i>et al</i> ^[52] , 2012; Zarate <i>et al</i> ^[76] , 2016; Pirotte <i>et al</i> ^[63] , 2010
BAF60A (SMARCD1)	Oligodendrocyte precursors	-	BRG1, BAF155 and BAF170	CSS, Nicolaides-Baraitser syndrome	(Yu <i>et al</i> ^[54] , 2013; Hsiao <i>et al</i> ^[53] , 2003; Machol <i>et al</i> ^[78] , 2019; Nixon <i>et al</i> ^[77] , 2019

BAF60C (SMARCD3)	NPCs in human retinas as well as mouse retina, cortex and spinal cord	Keeps progenitors in a proliferative state -	the Notch signaling	-	Lamba <i>et al</i> ^[55] , 2008
BAF155 (SMARCC1)	oNSC, adult human OBNSCs	Proliferation and maintenance of ONSCs forebrain development	and BRG1, PAX6	ASD	Lessard <i>et al</i> ^[41] , 2007; Marei <i>et al</i> ^[52] , 2012; Narayanan <i>et al</i> ^[33] , 2015; Neale <i>et al</i> ^[84] , 2012
BAF170 (SMARCC2)	oNSC, in postnatal DG, in RGL progenitors	oNSC proliferation, affects NSC proliferation, differentiation, forebrain development	BRG1	CSS, ASD, Nicolaides-Baraitser syndrome	Lessard <i>et al</i> ^[41] , 2007; Machol <i>et al</i> ^[78] , 2019; Narayanan <i>et al</i> ^[33] , 2015; Neale <i>et al</i> ^[84] , 2012; Tuoc <i>et al</i> ^[38] , 2017; Yi, Li <i>et al</i> . 2022)
BAF190A (BRG1/SMARCC A4)	Mouse VZ, SGZ, SEZ, NSCs/NPCs, NCC	NSC maintenance and neuronal differentiation	PAX6, BAF45D	CSS, ASD	Tsurusaki <i>et al</i> ^[72] , 2012; De Rubeis <i>et al</i> ^[85] , 2014; Matsumoto <i>et al</i> ^[28] , 2006; Petrik <i>et</i>

al^[29], 2015; Ninkovic *et al*^[30], 2013; Li, Xiong *et al.* 2013)

Tsurusaki *et al*^[72], 2012;
Liu *et al*^[40], 2021

BAF250A (ARID1A)	Developing cortex	Regulates proliferation and differentiation during cortical development	NSPC BSG1 CSS
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9

BRG1: Brahma related gene 1; BRM: Brahma; BAF: BRG1/BRM-associated factor; NSPCs: Neural stem/progenitor cells; oNSCs: Olfactory neural stem cells; CSS: Coffin-siris syndrome; VZ: Ventricular zone; OBNSCs: Olfactory bulb-derived neural stem cells; ASD: Autism spectrum disorder; KSS: Kleefstra syndrome spectrum; DG: Dentate gyrus; RGL: Radial glial-like; SEZ: Subependymal zone; NCC: Neural crest cells.

6%

SIMILARITY INDEX

PRIMARY SOURCES

- 1

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