# Epigenetic regulation by BAF (mSWI/SNF) chromatin remodeling complexes in late cortical development and beyond

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Affidavit

I herewith declare that the PhD thesis entitled ‘‘Epigenetic regulation by BAF (mSWI/SNF) chromatin remodeling complexes in late cortical development and beyond’’ was written independently, with no other sources and aids than quoted.

Goettingen, May 22th, 2019

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# Chapter 1: General Introduction

## 1.1. Epigenetic modifications in cell biological processes

Epigenetic modifications are defined as mechanisms that regulate gene expression without changes in the underlying DNA sequence (Bernstein *et al.*, 2007; Bird, 2007). In the mammalian cells, epigenetic modifiers can alter chromatin architecture and genomic function through different processes, including DNA, RNA or histone modifications, and activity of non-coding RNAs (Strahl & Allis, 2000; Goldberg *et al.*, 2007; Kouzarides, 2007).

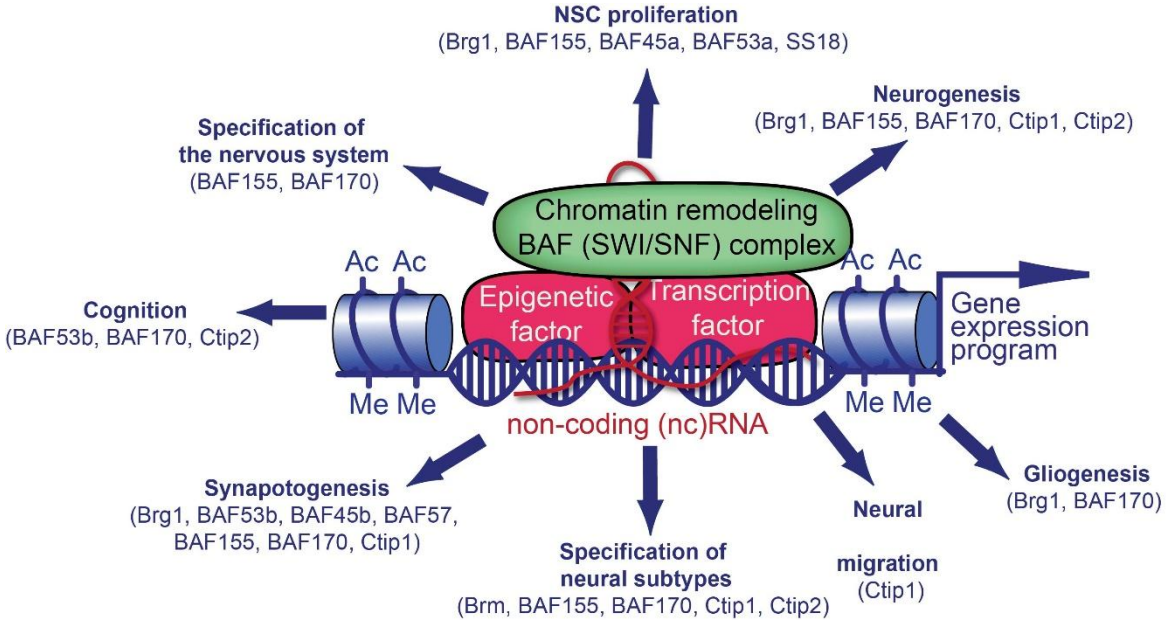


**Figure 1.1 Chromatin remodeling BAF (mSWI/SNF) complex in neural development.** The BAF complex, epigenetic factors and transcription factors (TF) control gene expression. TFs and ncRNAs bind to specific DNA sequences. The recruitment of BAF complexes and other epigenetic factors on the genome leads to altered epigenetic marks (e.g., histone acetylation, Ac; histone methylation, Me) and chromatin structure in order to activate or repress a specific gene expression program in cell lineages. This figure taken from Sokpor *et al*. (2017).

Normally, epigenetic modifiers that target chromatin work as a complex machinery to modulate higher-level chromatin configuration to impact many biological processes, including cell renewal, differentiation, motility, maturation, survival and

reprogramming (Figure 1.1) (Reik, 2007; Boland *et al.*, 2014; Sokpor *et al.*, 2017; Hanna *et al.*, 2018). The outcome of various epigenetic modifications broadly converges on either gene repression or activation. Generally, epigenetic regulators that promote gene expression activation remodel compact chromatin structure to an open or relaxed chromatin. The relaxed chromatin is known to be transcriptionally active because of related increase accessibility by transcription factors (Hirabayashi & Gotoh, 2010; Juliandi *et al.*, 2010; Coskun *et al.*, 2012; Ronan *et al.*, 2013; Yao *et al.*, 2016; Watson & Tsai, 2017). The converse is true for transcription repression being caused by chromatin modifiers that render the chromatin compact.

The epigenetic regulators of chromatin structure can be categorized into: covalent and non-covalent chromatin modifiers. Covalent modifiers regulate chromatin via processes including methylation, acetylation, phosphorylation and ubiquitination, whereas non-covalent chromatin modification includes ATP-dependent chromatin remodelers which have been implicated in regulating many developmental processes, including neurodevelopment (Strahl & Allis, 2000; Neilson *et al.*, 2006; Goldberg *et al.*, 2007; Tran *et al.*, 2013; Narayanan *et al.*, 2015a; Bachmann *et al.*, 2016b; Nguyen *et al.*, 2016; Nguyen *et al.*, 2018).

### 1.2. ATP-dependent chromatin modifiers

The ATP-dependent chromatin remodeling factors are multi-subunits complexes that depend on energy obtained from ATP breakdown to orchestrate detectable alterations in DNA-histone interactions that frequently translate in transcriptional changes to influence cellular developmental processes (Hirabayashi *et al.*, 2009; Yoo & Crabtree, 2009; Hirabayashi & Gotoh, 2010; Ho & Crabtree, 2010; Yao *et al.*, 2016; Albert *et al.*, 2017; Sokpor *et al.*, 2017). Mechanistically, chromatin remodeling involves nucleosomal mobilization that enhances the accessibility of DNA sequences to regulatory proteins that target genomic loci (Reinke & Hörz, 2003; Bailey *et al.*, 2011).

ATP-dependent chromatin remodeling complexes typically have ATPase subunits that allow them to hydrolyze ATP and to use the generated energy in order to remodel the chromatin structure. The mobilization of chromatin domains to alter DNA access is considered as a general mechanism that defines all ATP-dependent

chromatin remodelers (Clapier *et al.*, 2017). Based on similarities and differences in their ATPase domains and related subunits, the chromatin remodelers can be further classified into four categories of complexes: INO80/SWR, imitation switch (ISWI), chromodomain helicase DNA-binding (CHD)/Nucleosome Remodeling Deacetylase (NuRD), and switch/sucrose non-fermentable (SWI/SNF) (Flaus *et al.*, 2006).

My study focused on the SWI/SNF complex that have been shown to play indispensable role in embryonic development including neurodevelopment and neuropsychiatric disorders (Sokpor *et al.*, 2017).

### 1.3. Biochemical features of the SWI/SNF (BAF) Complex

The SWI/SNF complex was first identified in yeast to be composed of few subunits (Neigeborn & Carlson, 1984; Wang *et al.*, 1996a). However, the mammalian orthologs, mSWI/SNF, or the Brg1/Brm associated factor (BAF) complex is made up of about 15 subunits totaling about 2 Megadalton (MDa) in size (Lessard *et al.*, 2007; Wu *et al.*, 2007).

The BAF complex is typically found around gene promoters and enhancers, thus making them participate in gene expression programs that orchestrate cell biological processes including cell renewal, specification, differentiation and migration. Like other ATP-dependent chromatin remodelers, the BAF complex is composed of exchangeable ATPase catalytic core(s): either BRM/SWI2 related gene 1 (BRG1) or Brahma (BRM) depending on cell lineage (Neigeborn & Carlson, 1984; Wang *et al.*, 1996a; Lessard *et al.*, 2007; Wu *et al.*, 2007; Kadoch *et al.*, 2013). The BAF complex also contains other core subunits, including BAF155, BAF170 and BAF47 and variant subunits such as BAF60, BAF100, and BAF 250 that are ubiquitously expressed in the mammalian cell (Phelan *et al.*, 1999; Sokpor *et al.*, 2018). Some of variant subunits are expressed specifically in certain cell lineages such as BAF45A, BAF53A in neural stem cells and BAF45B, BAF53B in neurons (Bachmann, 2016; Lessard, 2007).