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The SWI/SNF complex subunit genes: Their functions, variations, and links to risk and survival outcomes in human cancers

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ABSTRACT

SWI/SNF is a multiprotein complex essential for regulation of eukaryotic gene expression. In this article, we review the function and characteristics of this complex and its subunits in cancer-related phenotypes. We also present and discuss the publically available survival analysis data for TCGA patient cohorts, revealing novel relationships between the expression levels of the SWI/SNF subunit genes and patient survival times in several cancers. Overall, multiple lines of research point to a wide-spread role for the SWI/SNF complex genes in human cancer susceptibility and patient survival times. Examples include the mutations in *ARID1A* with cancer-driving effects, associations of tumor SWI/SNF gene expression levels and patient survival times, and two *BRM* promoter region polymorphisms linked to risk or patient outcomes in multiple human cancers. These findings should motivate comprehensive studies in order to fully dissect these relationships and verify the potential clinical utility of the SWI/SNF genes in controlling cancer.

1. SWI/SNF complex and its function

Chromatin remodelling is one of the mechanisms essential in dynamic regulation of gene expression. In mammalians, this is performed by a number of different proteins/protein complexes (Muchardt and Yaniv, 1999). SWI/SNF is one of these complexes that was first identified in yeast when genes affecting the SWItch in mating type (Haber and Garvik, 1977) and Sucrose Non-Fermenting (SNF) phenotypes were identified (Neigeborn and Carlson, 1984).

The main molecular function of the SWI/SNF complex is chromatin remodeling through disruption of nucleosome. This requires recruitment of the SWI/SNF complex to DNA regions by transcription regulators and other proteins, upon which the SWI/SNF complex moves the nucleosomes along the DNA and modifies its accessibility. This in turn allows gene expression regulation − either suppression or activation − through binding of the transcriptional regulators to exposed DNA (Muchardt and Yaniv, 1999). In yeast, around 6% of the genes are estimated to be regulated by the SWI/SNF complex (Holstege et al., 1998).

Functional homologs of this protein complex were later identified in other eukaryotic organisms including Drosophila (Elfring et al., 1994) and mammalians (Wang et al., 1996). In contrast to yeast, the mammalian SWI/SNF complex exists in multiple forms that are characterized by different subunit compositions. These complexes usually include either BRM/SMARCA2 or BRG1/SMARCA4 (the ATPases that hydrolyze the ATP), and a set of 6–11 other proteins called Brg1/BRM associated factors (BAFs) that are essential for binding to DNA or proteins (Table 1). In humans, three of these subunits (INI1/SMARCB1, BAF155/SMARCC1, and BAF170/SMARCC2) are called "core subunits" as they are essential for the ATP-dependent chromatin remodelling activity of the SWI/SNF complexes together with BRM or BRG1 (Phelan et al., 1999). It has been suggested that the heterogeneity in SWI/SNF subunits/complex in higher eukaryotes allows the functional diversity required by the changing cellular needs and specialized functions of the differentiated cells (Wang et al., 1996; Ryme et al., 2009). Additionally, genome-wide analyses showed that in human cells SWI/SNF subunits bind in close vicinity to not only promoters but other regulatory regions, such as enhancers and DNA replication start sites (Euskirchen et al., 2011). Also, SWI/SNF subunits were found to bind to a number of proteins involved in nuclear and cytoskeletal organization. These findings indicate a potentially broader function for the SWI/SNF complex in human cells than solely transcriptional regulation (Euskirchen et al., 2011).

2. Functional characteristics of BRM and BRG1, the two SWI/SNF ATPases

Because of their ATPase function being critical for the function of

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Table 1
Human SWI/SNF subunits.

*Gene	*Subunit category of the protein product	**BAF/PBAF status of the protein product	**Mutually exclusive subunits	***Genomic location of the gene
BRM/SMARCA2	Helicase/ATPase	found in only BAF	Mutually exclusive with BRG1	9p24.3
BRG1/SMARCA4	Helicase/ATPase	found in both BAF and PBAF	Mutually exclusive with BRM in BAF	19p13.2
INI1/SMARCB1	Core subunit	found in both BAF and PBAF		22q11.23
BAF155/SMARCC1	Core subunit	found in both BAF and PBAF		3p21.31
BAF170/SMARCC2	Core subunit	found in both BAF and PBAF		12q13.2
BAF60A/SMARCD1	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF60 B and BAF60C	12q13.12
BAF60B/SMARCD2	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF60A and BAF60C	17q23.3
BAF60C/SMARCD3	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF60A and BAF60B	7q36.1
BAF57/SMARCE1	Accessory subunit	found in both BAF and PBAF	–	17q21.2
BAF53A/ACTL6A	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF53B	3q26.33
BAF53B/ACTL6B	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF53A	7q22.1
BAF250A/ARID1A	Accessory subunit	found in only BAF	Mutually exclusive with ARID1B	1p36.11
BAF250B/ARID1B	Accessory subunit	found in only BAF	Mutually exclusive with ARID1A	6q25.3
BAF180/PBRM1	Accessory subunit	found in only PBAF		3p21.1
BAF200/ARID2	Accessory subunit	found in only PBAF		12q12
BRD7	Accessory subunit	found in only PBAF		16q12.1
ACTB	Accessory subunit	found in both BAF and PBAF		7p22.1
BAF45A/PHF10	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF45B, BAF45C, and BAF45D	6q27
BAF45B/DPF1	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF45A, BAF45C, and BAF45D	19q13.2
BAF45C/DPF3	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF45A, BAF45B, and BAF45D	14q24.2
BAF45D/DPF2	Accessory subunit	found in both BAF and PBAF	Mutually exclusive with BAF45A, BAF45B, and BAF45C	11q13.1
#BCL7A	Accessory subunit	found in BAF		12q24.31
#BCL7B	Accessory subunit	found in BAF		7q11.23
#BCL7C	Accessory subunit	found in BAF		16p11.2
#BCL11A	Accessory subunit	found in BAF		2p16.1
#BCL11B	Accessory subunit	found in BAF		14q32.2
#SS18	Accessory subunit	found in BAF		18q11.2

*The first gene symbol is the one that is mostly used in literature, followed by the symbol assigned by the HUGO gene nomenclature committee (Bruford et al., 2008). Exceptions are the genes that are shown by one symbol only (which are the symbols approved by the HUGO gene nomenclature committee). **Based on Euskirchen et al. (2012), Wilson and Roberts (2011), or Kadoch et al. (2013). SWI/SNF complexes contain one of the helicases/ATPases, three core subunits (INI1, BAF155, and BAF170), BAF57, and ACTB in addition to a set of other proteins. Human BAF (BRG1 associated factors) and PBAF (polybromo BRG1-associated factor) are SWI/SNF complexes that differ in subunit composition; particularly BAF200, BAF180, BRD7 are only detected in PBAF, and BAF250A and BAF250B are only found in the BAF complex (Wilson and Roberts, 2011). Also note that the only helicase identified in PBAF is BRG1. BAF and PBAF are also known as SWI/SNF-A and SWI/SNF-B, respectively. Some of the accessory subunits are mutually exclusive (i.e. BAF60A, BAF60B, and BAF60C; BAF53A and BAF53B; BAF250A and BAF250B; and BAF45A, BAF45B, BAF45C, and BAF45D; (Wilson and Roberts, 2011)), thus do not present in the same complex. ***Based on UCSC genome browser (Speir et al., 2016). #These subunits are identified in a human T cell line (Kadoch et al., 2013). There are other mammalian SWI/SNF complexes identified with different subunit composition that are not shown here, including neural progenitor, neuron, and embryonic stem cell BAFs (reviewed in (Hohmann and Vakoc, 2014)).

the SWI/SNF complex, BRM and BRG1 have been subject to intense research from the beginning on. BRM and BRG1 show significant homology in their sequences (~75%) (Chiba et al., 1994) and some of the functional units (i.e. protein domains and motifs) are hence common to both proteins. For example, in BRM there is a N-terminus region rich in proline and glutamine residues (P/Q region), followed by a partially overlapping region characterized by charged amino acids, a helicase domain, and a C–terminus bromodomain (Muchardt and Yaniv, 1993). The BRG1 protein has a similar but slightly different structure, particularly in the N-terminal amino acid repeat region (Chiba et al., 1994). Both proteins also include a LXCXE/E7 homology motif that interacts with the RB family members (Dunaief et al., 1994; Strober et al., 1996). However, the greatest homology between BRM and BRG1 is observed in their helicase domain (86% homology) (Chiba et al., 1994). Interestingly, early studies on mammalian SWI/SNF complexes identified that BRM and BRG1 were mutually exclusive within the context of SWI/SNF function (Wang et al., 1996). Thus, despite their seemingly existing functional redundancy, there are notable differences as well as individual functional characteristics of these two ATPases, which deserve further discussion.

The majority of the insight into the functions of the mammalian BRM and BRG1 comes from the studies on mouse model systems. For example, while brg1 and brm were thought to be functionally redundant, their knock-out mouse models showed that lack of brg1 results in a relatively more severe phenotype. Specifically, homozygous deletion of brg1 results in early embryonic lethality in mouse (Bultman et al., 2000). In contrast, brm deficiency is not associated with embryonic death, even though it seems to be associated with the increased cell proliferation and tends to lead to increased mass in adult mice (particularly in bone, muscle, and connective tissues). This suggests that brm is not required for the mouse embryonic development or viability (Reyes et al., 1998). Additionally, heterozygous loss of brg1 leads to increased risk of developing cancer, suggesting that it is a tumor suppressor gene in mice (Bultman et al., 2000). In contrast, neither the homozygous nor heterozygous loss of brm *per se* is associated with the increased susceptibility to cancer in this organism (Reyes et al., 1998). This situation changes dramatically, however, when animals are exposed to carcinogens, such as ethyl carbamate, a chemical with known carcinogenic roles in lung tissue; under this conditions both heterozygous and homozygous loss of brm confers significantly increased risk of lung cancer in mice (Glaros et al., 2007). These results suggest that down regulation of brm can increase the risk for cancer under specific conditions. These findings also suggest that brm is a tumor susceptibility gene, rather than a tumor suppressor gene (Glaros et al., 2007) – this characteristic distinguishes it from other SWI/SNF subunits. Additionally, in mouse fibroblast cells, loss of brg1 but not of brm, was reported to be associated with aberrant mitosis, chromatin structure, and genomic instability (Bourgo et al., 2009). Another study that also used the mouse fibroblast cells found that the brm and brg levels show variability and this variability is cell cycle