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Hijacking the chromatin remodeling machinery: *impact of SWI/SNF perturbations in cancer*

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Abstract

There is increasing evidence that alterations in chromatin remodeling play a significant role in human disease. The SWI/SNF chromatin remodeling complex family mobilizes nucleosomes and functions as a master regulator of gene expression and chromatin dynamics whose functional specificity is driven by combinatorial assembly of a central ATPase and association with 10-12 unique subunits. While the biochemical consequence of SWI/SNF in model systems has been extensively reviewed, the present article focuses on the evidence linking SWI/SNF perturbations to cancer initiation and tumor progression in human disease.

The SWI/SNF family of chromatin remodeling complexes are master regulators of transcription factor action and resultant gene expression programs. SWI/SNF complexes are large, ~2 MDa multi-subunit conglomerates that serve to either enhance or suppress gene transcription through mobilization of nucleosomes(1, 2). Intriguingly, mounting evidence supports the paradigm that specificity of SWI/SNF action evolves through combinatorial assembly of 10-12 subunits, and that “imbalances” in subunit composition are frequently observed in human cancers. While the functions of SWI/SNF in transcriptional control and development have been extensively reviewed(1-6), the present study will focus exclusively on the role of SWI/SNF and its subunit dysregulation in tumorigenesis, disease progression, and therapeutic resistance.

Diversity in SWI/SNF composition: a brief overview

SWI/SNF subunits can be grossly sub-classified into three categories: *i)* enzymatic (ATPase), *ii)* core subunits, and *iii)* accessory subunits (7). While the precise mechanisms by which SWI/SNF modifies chromatin structure remain incompletely understood, this process is thought to involve ATPase-dependent disruption of histone-DNA association and resultant nucleosome “sliding”(2, 7). Accordingly, each SWI/SNF complex incorporates one of two possible ATPases, BRM (Brahma) or BRG1 (Brahma-Related Gene 1), that share 75% amino acid identity. Based on these observations, one might expect that the ATPases serve overlapping cellular functions and follow similar disruption patterns in human disease. By contrast, laboratory and clinical evidence, discussed within this article, suggest that the two ATPases frequently show differentially altered expression patterns and *in vivo* functions.

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Accompanying each ATPase are 10-12 proteins known as BAFs (BRG1 or BRM-associated factors) consisting of “core” and “accessory” subunits (Figure 1). The “core” subunits, BAF155, BAF170, and SNF5 (also referred to as SMARCB1, BAF47 or INI1), were functionally classified based on their ability to restore efficient nucleosome remodeling *in vitro*(8, 9). BAF155 maintains a scaffolding-like function, and can influence both stability and assembly of other SWI/SNF subunits(10). The function of BAF170, which shares homology with BAF155, is less well understood, but may also control the levels of other SWI/SNF subunits. Given these activities, the roles of BAF155 and BAF170 as core subunits can be readily conceptualized. By contrast, the function of SNF5 is divergent, as this subunit contains an intrinsic, non-specific, DNA-binding domain. Much emphasis has been placed on delineation of SNF5 action, as this subunit is a bona fide tumor suppressor gene in malignant rhabdoid tumor development, and regulates expression of critical proliferative control genes(11, 12). Thus, the core SWI/SNF subunits encompass widely distinct biochemical and functional activities.

The accessory subunits are hypothesized to dictate specificity of SWI/SNF complex function (1, 4). These subunits include BAF60a, b, and c, encoded by 3 distinct genes and present in only one copy per complex. The BAF45a-d and BAF53a and b accessory subunit classes are similarly encoded by multiple genes, but the relevance of each for overall SWI/SNF function and combinatorial assembly remains incompletely defined. Established demonstration of specificity arises from the BAF250a, b and BAF180 subunits, which define the BAF and PBAF versions of SWI/SNF complexes, respectively. BAF180 incorporation into SWI/SNF is mutually exclusive with the presence of BAF250a or BAF250b. Additional specificity factors with a suggested role in human disease include BAF57, BAF200, BAF53a, and beta-actin. Overall, the relative abundance and combinatorial assembly of these subunits has been elegantly compared to a chromatin-remodeling “language”, wherein the subunit ‘letters’ can be assembled into at least 288 distinct words, each with possible alternative cellular outcomes (1). In keeping with this concept, specific SWI/SNF combinations have been recently implicated with pluripotency and therefore deemed esBAFs(13). By contrast, it is apparent in human cancer that disease-associated ‘misspellings’ can contribute to disease initiation, progression, and metastasis.

Cancer initiation

Incontrovertible evidence supports the contention that SWI/SNF alterations contribute to tumorigenesis. Intriguingly, these alterations frequently entail tissue/tumor-specific loss of individual subunits, resulting in elimination of specific SWI/SNF complexes and possible creation of new combinatorial assemblies. While the biochemical consequence of SWI/SNF subunit loss is currently under active investigation, SWI/SNF misregulation appears to play a subunit and tissue specific role in cancer initiation (Figure 2).

ATPases: specialized tumor suppressors?

Extensive analyses support tissue and tumor-specific roles of SWI/SNF ATPase subunit loss in tumor development. Several reports have shown mutations and/or loss of BRG1 in human cancer cell lines and primary tumors (14-20). Supporting a role in cancer initiation, loss of heterozygosity (LOH) of the region surrounding *BRG* (21) occurs with significant frequency in human adenocarcinomas (22-27). Interest in this region is heightened by the presence of the Peutz-Jeghers multiple adenocarcinoma syndrome gene, *STK11/LKB1*, which maps 8.5 Mb distally from *BRG1*(26-30) (Figure 3). Importantly, chromosome transfer studies mapped tumor suppressor function to this region (31, 32), and at least one report localized the tumor suppressor gene to a region containing BRG1 but lacking STK11(32), thereby suggesting that selected cancers may arise from *BRG1* mutations rather than aberrant STK11 function. Alternatively, BRG1 loss could occur as a secondary event in a subset of tumors

that have deletions of the STK11 gene. Complementing these findings, studies in genetically engineered mice models (GEMM) showed that while germline loss of BRG1 leads to early embryonic lethality, *Brg1* heterozygous animals develop mammary adenocarcinomas due to haploinsufficiency (33, 34). Recent reports also demonstrated an increased frequency of lung adenocarcinomas in *Brg1*$^{+/-}$ mice exposed to the carcinogen urethane (35), and inactivating mutations of BRG1 have been identified in human lung cancer cell lines(36). Whether these results indicate that the reduced levels of BRG1 initiates tumor development in a rare population of cells or promotes tumor progression in a rare population of initiated cells remains unresolved, but provide strong indication that BRG1 possesses tumor suppressor functions.

Despite the molecular similarities in function between BRG1 and BRM, the pattern and influence of BRM loss on tumorigenesis is largely distinct from that of BRG1. Disparity in requirement for BRG1 versus BRM was first noted as a result of GEMM, wherein it was revealed that *Brm*$^{-/-}$ animals are viable, fertile, and slightly larger than wild-type littermates (37). Closer examination led to discovery of links between BRM loss and human disease. In the lung, exposure of *Brm*$^{-/-}$ animals to ethyl carbamate results in increased development of lung adenomas, thus implicating a role for BRM loss in lung cancer development(38). Further supporting this premise, BRM is downregulated in up to 30% of lung cancer cell lines analyzed, and is reduced at high frequency in both non-small cell lung adenocarcinomas and squamous cell carcinomas(18). These data provide compelling evidence for BRM loss as a contributory factor in lung tumorigenesis. Similar observations were deduced in examination of prostatic tissue, wherein loss of BRM has been identified in multiple studies as associated with prostatic adenocarcinoma (39, 40), and additionally shown to correlate with a higher proliferative index (40). These observations were further supported by examination of *Brm*$^{-/-}$ mice, wherein lobe-specific hyperplasia of the prostate was observed. In contrast to most observations in the lung, reduced SWI/SNF ATPase expression in the prostate was limited to the BRM subunit, and BRG1 expression was reported to be sustained at or above levels in non-neoplastic tissue. Striking parallels are observed in gastric cancer, wherein BRM loss correlates with histologic subtype(41). Examination of 27 cell lines and 89 primary tumors revealed that BRM loss is a significant marker of tumorigenesis, and promotes loss of villin, a well-established differentiation marker. Additional observations of BRM loss have been reported in esophageal, ovarian, bladder, colon, and breast cancer cell lines, but the impact of these events on tumor phenotypes has yet to be explored(42, 43). Nonetheless, these observations implicate BRM loss as a contributing factor and potential marker of tumorigenesis in lung, prostate, and gastric cancers. Together, these findings indicate that BRG1 and BRM ATPases serve specialized tumor suppressor like functions in human tissue.

Core subunits

Consistent with the consequence of ATPase subunit disruption, alteration of the selected core SWI/SNF subunits is associated with tumor initiation. The smallest core subunit, SNF5, behaves as a *bona fide* tumor suppressor gene. Mutations or deletions of the human *SNF5* gene (*SMARCB1*) were initially reported in >80% of renal and extrarenal malignant rhabdoid tumors (MRTs) (44). Subsequent analyses found loss of function mutations in nearly 100% of both renal and extrarenal MRTs and cell lines (45-47). Thus, multiple reports have established that mutations in this gene occur in the vast majority of sporadic human MRTs while germ line mutations are associated with non-penetrant familial MRT syndrome (44-55). Mutations in *SNF5* appear confined to a narrow range of tumors including MRTs, epithelioid sarcomas, renal medullary carcinomas, and recently, familial schwannomatosis (54, 56-58). Other reports have also implicated SNF5 loss in the development of choroid plexus carcinomas (59, 60). As would be expected based on these

clinical observations, complete loss of SNF5/INI1 expression leads to early embryonic lethality in GEMM (61-63). However, *Snf5/Ini1*$^{+/-}$ mice develop tumors with features of human MRTs in up to 60% of the animals beginning at 8 months (61-64). A conditional mutant that causes only partial penetrance of SNF5 leads to tumor development in 100% of the mice by 13 weeks (64). These results clearly establish that the *SNF5* gene acts as a classical tumor suppressor gene and initiates tumor development in a similar fashion to the *RB1*, *BRCA1* and *APC* genes.

As noted above, the remaining core subunits of BAF155 and BAF170 have been shown to regulate assembly and overall levels of other SWI/SNF subunits (10, 65). Therefore, one might predict that loss of either subunit might initiate tumor development or fuel tumor progression. As yet, there is little evidence linking BAF170 to human cancers. BAF155, however, resides in a region of chromosome 3, band p21.31, that includes other suspected tumor suppressor genes, such as *SEM3B* and *FUS1* (66, 67). Surprisingly, BAF155 is markedly induced in prostate cancer, and correlates with both tumor recurrence and dedifferentiation (68). Moreover, recent reports have found *increased* expression of BAF155 mRNA in cervical intraepithelial neoplasia (CIN), prostate cancer and colorectal cancer (68-71). However, the increased BAF155 mRNA levels were found in early stage dysplastic cervical lesions and were associated with a significantly better overall survival rate (70). These collective findings could indicate that aberrations in overall BAF155 levels may contribute to tumor initiation, dependent on context. Given the ability of BAF155 to control levels of other SWI/SNF subunits, it is intriguing to speculate that deregulated BAF155 expression may result in markedly altered availability of SWI/SNF subunits and a shift in the possible combinatorial assemblies. Based on these collective findings, it has become clear that while the loss of one core subunit, SNF5, can promotes tumorigenesis in a subset of human tissues, changes in expression in the BAF155 subunit may inhibit or promote tumor initiation or progression in cell or tissue specific manner.

Accessory subunits

Consistent with the posit that there is selective pressure in human cancer for alterations in SWI/SNF complex function, cancer-associated perturbations in expression have also been reported for the BAF250a, BAF180, BAF60, and BAF57. In a functional screen of 4 primary breast tumors and 3 primary prostate tumors, Huang et al. identified a deletion in the BAF250a gene (72). At what stage this event contributes to tumorigenesis remains untested, although functional studies have implicated BAF250 complexes as master regulators of cellular proliferation (73). Preliminary evidence also points toward a role for BAF180 and BAF60 subunits in proliferative control and tumor prevention. Truncating mutations in the BAF180/PBRM1 gene were identified in 2 human breast tumor cell lines and in 2/52 primary breast tumors, and functional analyses revealed that these mutations induce loss of cell cycle regulatory activity (74). Concordant with these observations, multidimensional LC-MS/MS identified reduced BAF180 protein expression in HNSCC compared to normal head and neck controls (71). As for the BAF60 subclass, BAF60a interacts directly with the p53 tumor suppressor, and in model systems supports both p53-mediated apoptosis and cell cycle arrest signals(75). Reduced BAF60c gene expression was associated with early stage neuroblastoma(76), therefore providing preliminary evidence that BAF60 subunits may be lost or downregulated in selected tumor types. Lastly, alterations in BAF45d have been primarily implicated in breast cancer, as SNPs in the 5' region of the gene are associated with increased risk, lymph node metastases, and tumor burden(77). Collectively, these observations point toward a role for BAF250a, BAF60a/c, BAF180, and BAF45d in tissue-specific tumor prevention.

In contrast, the role of the BAF53a and BAF57 accessory subunits appears variable. BAF53a interacts with p53 and assists in $p21^{CIP1}$ induction(78), implicating this subunit in

the cytostatic response to DNA damage. However, BAF53a is requisite for the oncogenic funtion of c-Myc, and is itself associated with mitotic chromosomes(79). The impact of these functions on tumor phenotypes awaits further investigation, as does analyses of BAF53a expression in human disease. Interestingly, the BAF57 subunit has been shown to harbor enhanced expression or activity in human tumors, especially with regard to the hormone-dependent cancers. In breast cancer cell lines, mutations in BAF57 were reported which increased the response of the estrogen receptor to a critical transcriptional cofactor, SRC1(80, 81). The frequency of these mutations and impact on breast cancer development or phenotypes awaits further analyses. In prostate cancer, BAF57 binds and facilitates activity of the androgen receptor (AR), a nuclear receptor and essential factor for prostate cancer development(82). Notably, studies reported elevated BAF57 levels in a subset of primary and lymph node prostate cancers, lending preliminary credence to the supposition that BAF57 function may be enhanced in steroid-hormone receptor dependent tumor types(83). Similar to observations with BAF180, these results suggest that elevation or gain-of-function alterations in BAF57 may significantly influence SWI/SNF function and confer pro-tumorigenic properties to the resulting complexes. Together, these intriguing findings suggest that unlike the central ATPases, loss or gain of specific accessory subunits may assist in cancer initiation, and provide the impetus to discern the consequence of altered subunit expression on SWI/SNF assembly and tumor endpoints.

Progression and therapeutic response: *unique roles for the ATPases*

While the majority of published SWI/SNF studies have probed the consequence of subunit dysfunction for tumorigenesis, emerging evidence is indicative of specialized SWI/SNF subunit roles in tumor progression and therapeutic response. Global diminution of SWI/SNF activity (via loss of BRG1 and BRM) in non-small cell lung carcinoma correlates with poor overall survival, providing some of the strongest indication that overall SWI/SNF activity protects against tumor progression (15, 18). For BRG1, several lines of evidence support the notion that its loss can contribute to neoplastic development during later stages rather than in early steps. For example, *Brg1*$^{+/-}$ mice develop mammary adenocarcinomas at a low penetrance (~12%) at approximately 12 months, despite showing no LOH in the tumors (33, 34). These results suggest that reduced BRG1 may allow a rare population of initiated cells to progress to neoplasia; otherwise, one would expect a more fulminant tumor phenotype in the *Brg1*$^{+/-}$ mice considering the haploinsufficient phenotype of the mammary tumors. While many human tumor cell lines lack detectable BRG1 and BRM expression, BRG1-deficient mouse fibroblasts and embryonal carcinoma cells paradoxically fail to proliferate or grow poorly in culture (33, 35, 84), and show dissolution of chromatin structure (Buorgo et al., in press). Apoptosis was observed in lung epithelia in vivo after deletion of both *Brg1* alleles (35). Taking these observations into account, it has been hypothesized that acquisition of cooperative genetic events during cellular transformation is needed to allow proliferation in the absence of BRG1 and BRM. Further supporting the notion that BRG1 loss can contribute to tumor progression, high frequency of LOH (75%) in NSCLC was shown to occur in late stage and metastatic samples but not early stage disease (25). Most dramatically, loss of BRG1 expression in acute lymphoblastic leukemia (ALL) strongly correlated with therapeutic resistance to prednisolone, and subsequent in vitro modeling showed that BRG1 knockdown was sufficient to achieve therapy resistance (85). Some parallels with SNF5 are noted, as downregulation of this subunit has also been linked to steroid resistance in ALL (85-87). While the resultant tumor phenotypes are distinct in different tissues, these data strongly support a role for BRG1 loss in tumor progression.

Unique profiles of loss and tumor progression were also observed with the BRM ATPase. Exemplifying the distinction between subunits, BRM but not BRG1 loss is a hallmark of the “poor” (poorly differentiated) form of gastric cancer, which is associated with unfavorable

prognosis (41). Mouse models also hint toward a link between BRM loss and therapeutic response in prostate cancer, as *Brm* deletion resulted in modest androgen-independent cellular proliferation of selected prostatic epithelia *in vivo* (40). Since androgen deprivation is the first line of therapeutic intervention for patients with disseminated disease, and the ability of tumors to circumvent androgen ablation (referred to as the transition to castration-resistant prostate cancer) represents an incurable phase, investigation of BRM loss on this event warrants further investigation. BRM status and response to hormonal-based therapies may also be of interest in breast cancer, since BRM is critical for the *in vitro* response to tamoxifen (88). BRM may also modify the response to genotoxic stress, as BRM loss alters DNA damage checkpoints *in vitro* (37), and loss of BRM occurs as an early response to ionizing radiation in esophageal squamous cell carcinomas. Most significantly, BRM loss was identified as an indicator of poor prognosis in non-small cell lung cancer. Patients with lung adenocarcinomas or squamous cell carcinomas incurred a 5-year survival rate of 72% if positive for BRM and BRG1, but only 32.3% if deficient in BRM or BRG1. Intriguingly, altered subcellular (membrane) localization of BRM was associated with a 16.7% survival rate (15). These findings are striking, as of 12 chromatin remodeling proteins examined, only BRM showed prognostic significance. Based on these findings, it is clear that the mechanisms by which BRM alters therapeutic response and alters the course of disease should be determined.

Despite the evidence linking ATPase alterations to tumor development and progression, few studies have addressed the impact of SWI/SNF function on invasion and metastasis in the clinic, and the GEMM provided little evidence linking loss of SWI/SNF to a metastatic phenotype. Therefore, only *in vitro* studies have provided clues regarding a potential role for alterations in complex subunit expression in metastasis. *In vitro* restoration of BRM in BRM-deficient lung cancer cells resulted in reduced soft agar and invasion capabilities(38), thus giving some indication that BRM may influence lethal tumor phenotypes. Additionally, BRG1 and/or BRM can regulate the expression of proteins associated with metastatic spread in a variety of human cancers, including CD44, CDH1 and actin filament organization (89-91). While these findings are provocative, further studies are needed using primary human tumor material and GEMM to definitively address the role of the SWI/SNF ATPases in the metastatic phenotype.

Within the core and accessory subunit categories, scant evidence exists to determine whether these subunits contribute to tumor progression. A recent report showed that loss of SNF5 protein expression occurs in renal medullary carcinoma, a rare malignancy associated with young adults, or in children with sickle cell trait or disease (92). In the case of MRT, it could be argued that SNF5 loss may play a role in tumor progression because no other report of additional genetic defects has appeared in the literature (93). However, most studies have examined only primary tumors and MRT cell lines and may have missed secondary genetic events. Progressive disease, metastases, and recurrences should be examined and compared with primary disease so that later events can be examined. For the accessory proteins, the individual subunits show widely varied influences on progression and treatment. Interestingly, BAF57 was recently identified in a high-throughput shRNA library screen as one of 5 genes (along with SNF5) required for the response of CML to imatinib(94). The same study identified BAF250a as required for the response to Fas ligand, thus further implicating the SWI/SNF subunits as putative effectors of chemotherapy. BAF45a, although known for a role in neural progenitor cells(7), was recently identified in a gene signature indicating favorable prognosis in colorectal cancer.

Based on these findings, it can be concluded that the SWI/SNF ATPases appear to have significant, disparate roles in protecting against tumor progression. The requirement of

individual cooperating subunits for these functions will be of the utmost importance to discern.

Conclusions and future directions

Based on the published observations described herein, it is evident that perturbations in SWI/SNF expression and function play substantive, subunit and tissue specific roles in human cancers. As such, several critical questions should be addressed. *First, what is the basis of BRG1 and BRM-associated anti-tumorigenic functions?* Loss of a central ATPase BRG1 or BRM, appears to significantly contribute to both tumor development and tumor progression, dependent on context, and emerging evidence supports a role for ATPase loss in promoting therapeutic resistance. While these findings identify BRG1 and BRM as candidate tumor suppressors, it remains unclear how these properties are exerted at the cellular level. *Second, what is the impact of a single ATPase loss on the formation of remaining SWI/SNF complexes?* This is a critical question, as current clinical evidence suggests that loss of only one ATPase is typically observed, thus leading to speculation about whether it is loss of that subunit or alterations in the remaining complexes that is tumor driving. For example, in tumors that select for BRM loss, remaining SWI/SNF complexes must shift to rely on BRG1-driven SWI/SNF chromatin remodeling. It should be determined how these alterations might alter the number and composition of resultant BRG1-associated complexes, and whether it is loss of BRM per se or “re-wiring” or increased levels of BRG1-associated complexes that promotes tumor phenotypes. *Third, how do perturbations of accessory or core subunits alter tumorigenesis or progression?* Although SNF5 has been confirmed as a specific tumor suppressor, the underlying mechanisms of action remain incompletely defined. Moreover, it is unclear how elimination of a core subunit may alter the function of remaining SWI/SNF complexes. Similar questions arise for BAF250a, BAF180, BAF60, BAF155, and BAF57, for which gains and losses have been shown to promote tumorigenesis in disparate tissues. *Fourth, what mechanisms drive tumor-specific subunit alterations?* Because substantial evidence supports the notion that different tumor types select for differential SWI/SNF subunit perturbations, we must determine what pro-tumorigenic properties each subunit alteration confers, and how these support tumor growth in a particular tissue environment. *Fifth, what is the basis of imbalances in SWI/SNF subunit expression?* While there is some evidence for genetic mutation and LOH, in most cases the basis of subunit loss or gain remains undefined. Investigation of such may provide important clues as to cooperating factors and mechanisms of alteration that promote human disease. *Sixth, are there emerging global paradigms that explain these seemingly disparate observations about the role of the SWI/SNF complex in human tumorigenesis?* Despite the apparent context- and tumor-specific differences found by different investigators, we find some potential areas of overlap. One fruitful area of investigation may lie in the well-established link between the SWI/SNF complex and nuclear receptor activity (95). Several studies have shown the effects of SWI/SNF complex alterations on estrogen and androgen signaling in human tumor cell lines (80, 82, 83, 96). Other reports showed a role for nicotinic acetylcholine receptors in NSCLC development, where BRG1 and BRM loss occurs frequently (97). A link has also been established between the loss of SWI/SNF complex function and epigenetic alterations in human tumor cell lines (90). This raises the interesting possibility that alterations in SWI/SNF complex activity could promote “epigenetic instability” in different human cancers, dependent upon the subunit loss. *Lastly, what are the clinical ramifications of overall SWI/SNF “imbalances” taking all subunits into account?* Early evidence has implicated imbalances in individual subunits with critical outcomes such as tumor development, proliferation, metastasis, therapy resistance, and patient survival. It should be determined if profiling of multiple SWI/SNF subunits provides greater prognostic or predictive value, and how these observations might be most effectively harnessed for clinical utility. In sum, hijacking of

SWI/SNF function clearly provides a powerful tool through which tumor cells can re-wire gene transcription and promote tumorigenesis; further investigation of this process is expected to reveal new nodes of possible therapeutic intervention.

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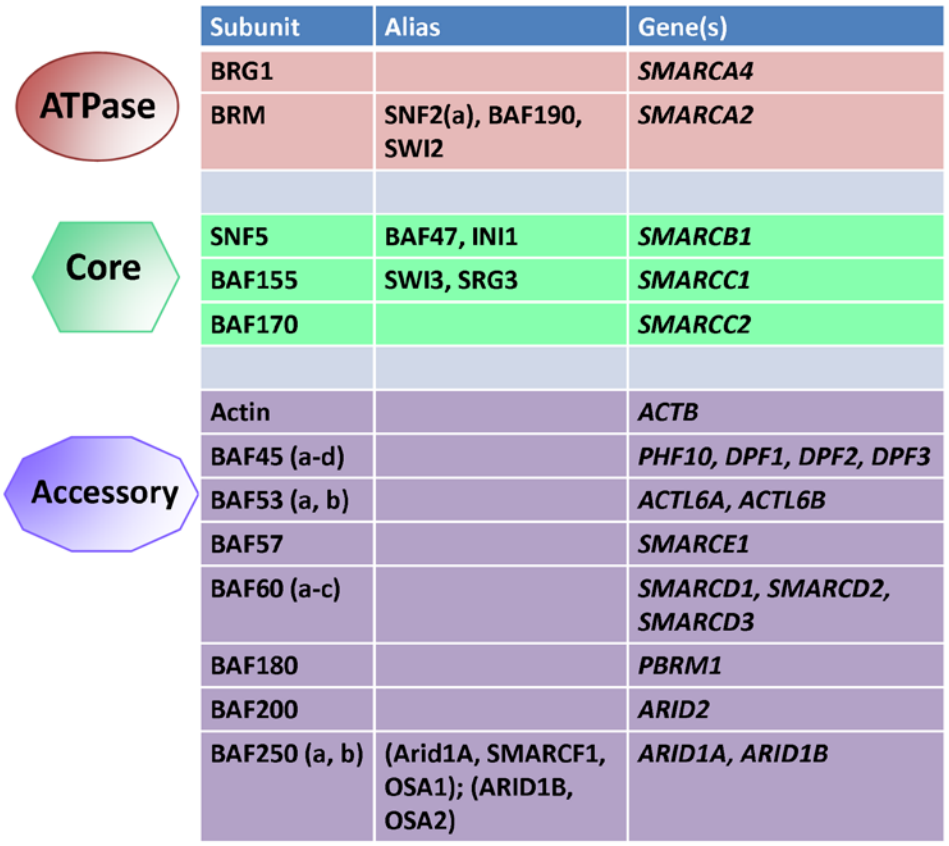

Subunit	Alias	Gene(s)
BRG1		*SMARCA4*
BRM	SNF2(a), BAF190, SWI2	*SMARCA2*
SNF5	BAF47, INI1	*SMARCB1*
BAF155	SWI3, SRG3	*SMARCC1*
BAF170		*SMARCC2*
Actin		*ACTB*
BAF45 (a-d)		*PHF10, DPF1, DPF2, DPF3*
BAF53 (a, b)		*ACTL6A, ACTL6B*
BAF57		*SMARCE1*
BAF60 (a-c)		*SMARCD1, SMARCD2, SMARCD3*
BAF180		*PBRM1*
BAF200		*ARID2*
BAF250 (a, b)	(Arid1A, SMARCF1, OSA1); (ARID1B, OSA2)	*ARID1A, ARID1B*

Figure 1. SWI/SNF subunits

Distinct SWI/SNF complexes are formed by combinatorial assembly of a central ATPase (pink), the core subunits (green), and selected accessory subunits (purple). Aliases and gene identifications for each known subunit are provided.

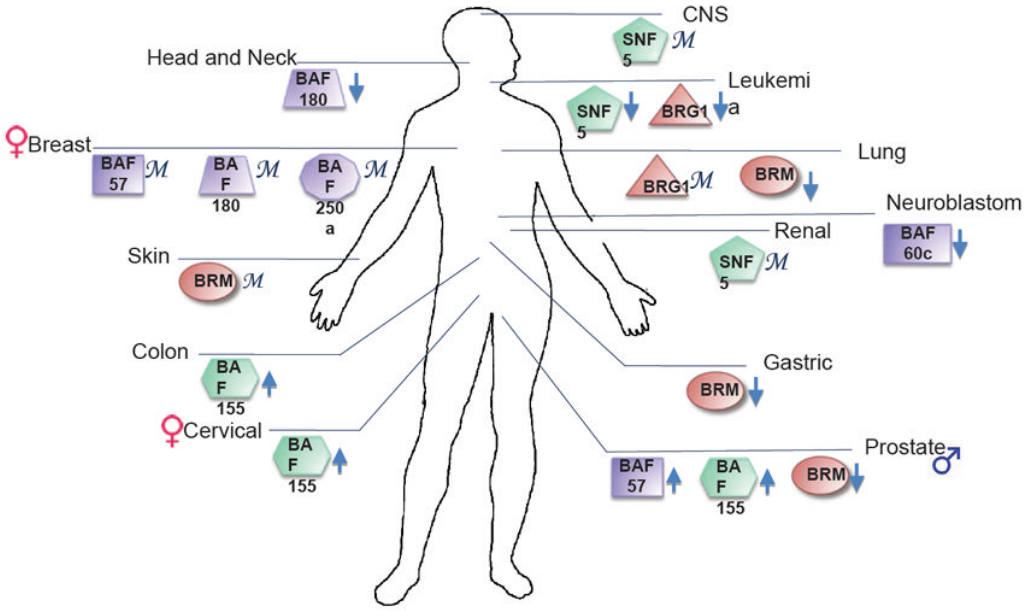

Figure 2. SWI/SNF alterations in human disease

Aberrant SWI/SNF expression has been reported in many tumor types. Alterations are summarized as shown. Arrows indicate enhanced or decreased expression. *M* indicates mutation.

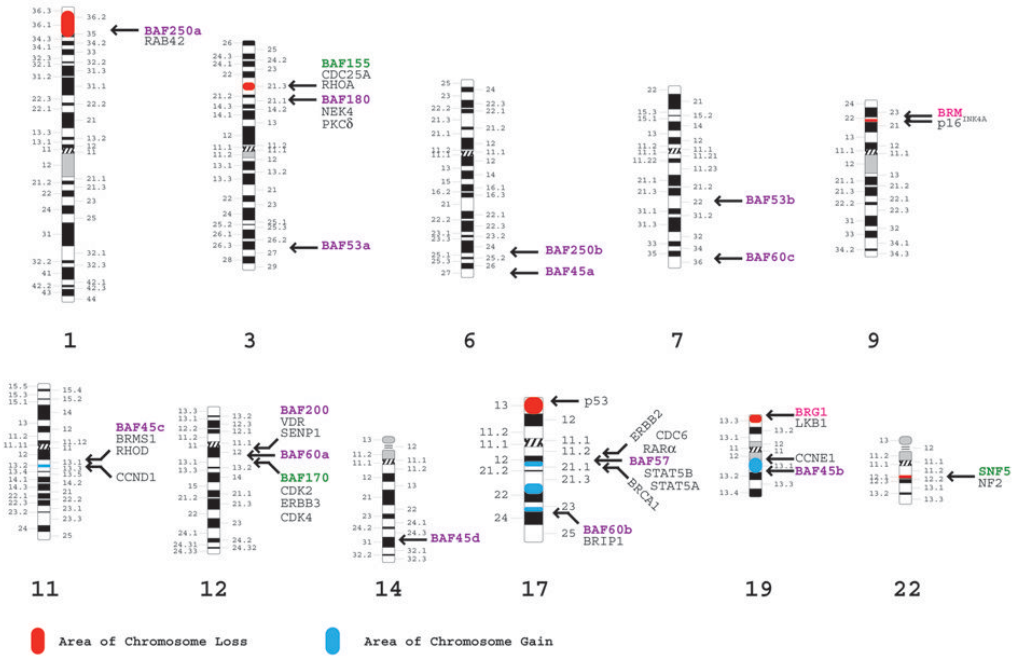

Figure 3. Ideogram of SWI/SNF subunit alterations in selected tumor types

Chromosomal locations of individual subunits are shown, and colors correspond to subclassifications shown in Figures 1 and 2. Areas of chromosomal gain are shown in blue and chromosomal loss in red. Areas of chromosomal gain and loss are not a complete survey of all human tumors, but represent data from tumors associated with SWI/SNF alterations including prostate, breast and NSCLC. Adjacent genes of cancer relevance are as indicated.